Chronic Fatigue Syndrome: The Roles of Perfectionism and Metacognition in Co-morbid Depression and Anxiety

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Introductory Chapter (Thesis Overview)

This thesis aims to increase clinical understanding of depression and anxiety in people living with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), a disabling long-term condition for which there is currently no known cure. Two clinical papers are presented. Each examines potentially relevant psychological mechanisms.

Due to the lack of effective medical treatments for CFS/ME, clinical focus is presently the management of physical symptoms, primarily with a view to reducing levels of fatigue (White et al., 2011). At a research level, there has been greater examination of factors associated with fatigue, with associated depression and anxiety being under-researched. This is despite the high levels of reported co-morbidity (Larkin & Martin, 2017), and evidence for the dynamic interplay between mental and physical health (Kiecolt-Glaser et al., 2002)

The role of psychology in supporting people with CFS/ME is mired in controversy. Examination of co-morbid mental health difficulties in CFS/ME has been hampered by symptomatic overlap with depression (Griffith & Zarrouf, 2008), methodological concerns regarding previous psychological research and treatment (Laws, 2017; Vink & Vink-Niese, 2019) and concerns raised by patient activist groups (Kelland, 2019). On the one hand, critics caution of the 'psychologisation of physical illness' (Gaudsmit & Gadd, 1991; Richman & Jason, 2001); on the other, the rejection of psychology as a relevant discipline risks neglecting the research and treatment of co-morbid mental health difficulties. Greater understanding of associated psychological factors could inform the development of evidence based, CFS/ME specific therapeutic interventions, aimed at reducing co-morbid depression and anxiety. Such targeted interventions would complement a multi-disciplinary approach to CFS/ME and would not seek to refute potentially underlying organic pathology.

Potentially predisposing personality traits has been one controversial area of research into CFS/ME. Perfectionism has attracted attention (Kempke et al., 2015), driven in part by clinical observations (Surawy et al., 1995) and arguably stereotyping (Deary & Chalder, 2008). However, this may remain a valid area of research with regards to co-morbid depression and anxiety; perfectionism has been found to be a trans-diagnostic risk factor for a range of both physical and mental health conditions (Egan, Wade, Shafran, 2011), and higher levels of perfectionism have been evidenced in people living with CFS/ME (White & Schweitzer, 2000). It is therefore clinically important to consider the potential relationship between perfectionism and emotional distress in physical health populations, including CFS/ME. However, research to date has focussed on the relationship between perfectionism and fatigue, as well as perfectionism as a predisposing risk factor for CFS/ME. Within the CFS/ME population, the association between perfectionism and depression and/or anxiety is under-researched, hence the selection of the question addressed in Chapter 1: What is the relationship between perfectionism and co-morbid depression and anxiety in people living with CFS/ME?

Chapter 1 systematically reviews the existing evidence of a relationship between perfectionism and either depression or anxiety, in this patient group. This process identified 7 relevant studies reported in 8 papers. Several factors of perfectionism were explored. Consistent with the wider literature and psychological theory, narrative synthesis indicated maladaptive perfectionism was consistently associated with depression. However, evidence for associations with other aspects of perfectionism was inconsistent. The relationship between perfectionism and anxiety in CFS/ME was identified as an under-researched area.

The review was prepared for submission to the Journal of Psychosomatic Research and formatted accordingly (see Appendix A). The journal was chosen because of its focus upon the relevance of psychological processes in physical health. Findings of the review are intended to

guide directions for future research, in addition to therapeutic interventions which seek to reduce depression in this patient group.

Chapter 2 examines the potential applicability of the Self-Regulatory Executive Function (S-REF) model of emotional distress (Wells & Matthews 1994) to understanding depression and anxiety experienced alongside CFS/ME. This model predicts that prolonged distress arises not from symptom-related appraisals or thought content per se, but rather metacognitive beliefs about worry and/or rumination, which drive unhelpful thought processes and responses; this is termed the cognitive-attentional syndrome (CAS; Wells & Matthews 1994). Two types of metacognitive belief are theorised to be of particular importance in activating and maintaining the CAS: positive metacognitive beliefs about the usefulness of worry, e.g. 'Worrying helps me cope', and negative metacognitive beliefs about the uncontrollability and danger of worry, e.g. 'When I start worrying, I cannot stop'.

The study found metacognitive beliefs accounted for a significant proportion of the variance in both depression and anxiety, when controlling for demographic and clinical variables including level of fatigue. Negative metacognitive beliefs, lack of cognitive confidence and cognitive self-consciousness and the CAS emerged as significant independent statistical predictors of depression. Positive metacognitive beliefs, negative metacognitive beliefs and the CAS emerged as significant independent statistical predictors of anxiety.

Overall, results provided support for the S-REF model. The relationship between positive metacognitive beliefs and depression was fully mediated by the CAS. Relationships between negative metacognitive beliefs and both depression and anxiety, and positive metacognitive beliefs and anxiety were partially mediated by the CAS.

The paper is intended for submission to the British Journal of Health Psychology (Appendix B), selected due to the focus on all aspects of psychology related to health, including

the management of chronic illness. Findings are intended to have implications for clinical interventions, specifically aiming to reduce co-morbid anxiety and/or depression in people living with CFS/ME.

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Chapter 1: Literature Review

Perfectionism, Depression and Anxiety in Chronic Fatigue Syndrome: A Systematic Review.

Running head: Perfectionism, Depression and Anxiety in CFS

Perfectionism, Depression and Anxiety in Chronic Fatigue Syndrome: A Systematic Review.

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Abstract

Objective: High levels of depression and anxiety are experienced by people living with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). The psychological mechanisms that cause and maintain distress in this context are not well-understood. One such mechanism may be perfectionism, a multifactorial, transdiagnostic risk factor for various physical and mental health conditions. This systematic review aimed to assess the nature of the relationship between perfectionism and depression and/or anxiety (emotional distress), in people living with CFS/ME.

Method: Systematic literature searches were completed using a combination of terms for 'perfectionism', 'emotional distress' and 'CFS/ME'. Inclusion was contingent upon publication in English in a peer-reviewed journal, and reporting of quantitative data pertaining to the relationship between perfectionism and depression and/or anxiety in adults (aged 18-65 years) with a clinical diagnosis of CFS/ME.

Results: Seven studies, reported in eight papers, were included. Only one study examined the relationship between perfectionism and anxiety; the remainder focused on depression. Only maladaptive perfectionism was consistently associated with depression, with studies reporting moderate-strong correlations. Findings regarding other aspects of perfectionism were mixed. Methodological limitations in selected studies related to sample size justification and selection, in addition to control of potential confounders; no studies controlled for fatigue in assessing the relationship between perfectionism and anxiety/depression.

Conclusion: Maladaptive perfectionism is associated with depression in patients with CFS/ME. The relationship between perfectionism and anxiety is under-researched in this patient group. Examining the dynamic interplay between maladaptive perfectionism, fatigue and both depression and anxiety may increase clinical understanding. This may be enhanced through

investigating psychological mechanisms through which the trait of perfectionism may influence distress.

Key words: Chronic Fatigue Syndrome, Perfectionism, Anxiety, Depression, Emotional Distress.

Introduction

Chronic Fatigue Syndrome (CFS) is a disabling long-term condition, characterized by medically unexplained, persistent fatigue which is new in onset, unalleviated by rest and exacerbated by physical or mental activity [1,2]. Historically, and across cultures, many terms describe CFS [3]. Although controversy surrounds whether CFS and Myalgic Encephalomyelitis (ME) are discrete or hybrid diagnoses [4, 5], this review uses the term 'CFS/ME', reflecting National Institute for Health and Care Excellence (NICE) guidelines [6] and current treatment pathways in the United Kingdom.

Presently, there is no objective test or consistent bio-marker for CFS/ME [7] and consistent organic explanations remain elusive [8 - 10]. Whilst consensus exists regarding the centrality of fatigue, variations exist between diagnostic criteria regarding the number, type and severity of additional symptoms [8]. Prevalence estimates range between 0.2% and 2.6% of the general population [11, 12] dependent upon case definition [13]. Lifetime prevalence is approximately 0.83% [14]. Approximately three quarters of people with CFS/ME are female [15]. Peak incidence occurs between the ages of 40-49 [16]. Symptom severity varies considerably both between patients and over time [6], making prevalence estimates by severity problematic [17]. Approximately 60% of people experience 'mild' symptoms at any one time [18]. The 10-29% most severely affected require significant bed rest and care [17]. Regardless of severity, full recovery is rare; 82% to 95% of people experience life-long symptoms [19, 20] and an increased need for health care provision [23].

Onset can be triggered by acute physical and/or psychosocial stressors [24], suggesting the utility of a bio-psychosocial model in understanding CFS/ME [25]. This model has been criticised for its emphasis on psychological factors [26]. However, psychoneuroimmunology research indicates reciprocity between physiological functioning and emotional distress in several health

conditions [27], which could apply to CFS/ME [28]. Irrespective of aetiological debate, co-morbid depression and/or anxiety are frequently experienced [29]. Between 36%-70% of patients experience depression [30,31] and 32%-57% experience anxiety [32,33]. These co-morbidities can lead to poorer prognosis [34] and potential exacerbation of physical impairment [35]. Understanding modifiable psychological processes linked to anxiety and depression in CFS/ME is necessary to develop more effective interventions. Perfectionism, a transdiagnostic risk factor for a range of physical [36] and mental health conditions [37 – 42] could be an important determinant of anxiety and depression in CFS/ME.

Perfectionism is a relatively stable, multifactorial construct, consisting of excessive performance standards and critical self-evaluation [36, 39, 43]. A dual-process model of perfectionism differentiates between ‘adaptive’ and ‘maladaptive’ perfectionism [43, 44]; the former is motivated by a desire to achieve goals, whilst the latter is driven by a need to avoid failure [44, 45]. Adaptive and maladaptive perfectionism relate differentially to health and wellbeing [36]. Within the general population, depression and anxiety are positively correlated with maladaptive perfectionism [43, 46] whilst links with adaptive perfectionism are inconsistent [47].

Maladaptive perfectionism manifests in cognitive, emotional, behavioural, and physiological responses [48] which can lead to emotional and physical exhaustion, as well as physical symptoms through overburdening the stress response system [49-52]. Behavioural components of maladaptive perfectionism may be motivated by a fear of failing to meet standards, resulting in either anxiety-driven over-work [48] or procrastination where standards are impossible to meet [38, 53]. Perceived failure to meet the standards of an ideal self may increase vulnerability to depression, through overemphasizing productivity and accomplishment in assessing self-worth [54, 55]. The ensuing distress maintains vulnerability to physical symptoms

via prolonged autonomic arousal [24]. Once physically unwell, bursts of activity to meet unrealistic, pre-morbid standards are often punctuated by post-exertional malaise and the need to recuperate [56].

Higher levels of maladaptive perfectionism occur in people living with CFS/ME compared to healthy controls [57]. Maladaptive perfectionism has also been positively associated with self-critical coping strategies and adjustment difficulties in this patient group [58]. Perfectionism is a shared risk factor for depression, anxiety [59] and CFS/ME [60,61], suggesting the prudence of investigating associations between perfectionism and depression/anxiety within a CFS/ME population. To date, however, research has primarily focussed on the relationship between perfectionism and fatigue [60, 62] and perfectionism as a predisposing factor to CFS/ME [61].

Greater understanding of the relationship between perfectionism and depression/anxiety in the CFS/ME population may inform a 'living well with chronic illness' approach, tailored to individual presentation. This would seek to reduce the emotional distress experienced alongside physical symptoms regardless of aetiological debate, as well as promoting adjustment to physical illness and adaptive coping strategies. The aim of this systematic review, therefore, is to investigate the magnitude of the relationship between perfectionism and depression/anxiety in people living with CFS/ME.

Methods

Conduct and Reporting

Conduct and reporting adheres to recommendations by the Centre for Reviews and Dissemination (CRD) [63] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance [64]. A protocol can be accessed at: https://www.crd.york.ac.uk/PROSPERO, ID: CRD4201912483.

Search Strategy

Four electronic databases (CINAHL, MEDLINE, Scopus, PsycINFO) were systematically searched for relevant peer-reviewed articles from their inception until December 2019, using the following search terms: chronic fatigue* OR myalgic encephalomyelitis OR CFS OR M.E OR post viral* OR post-viral* OR PVFS OR chronic fatigue and immune dysfunction* OR CFIDS OR neuromyasthenia OR benign myalgic encephalomyelitis OR akureyri disease AND depress* OR anxi* OR distress* OR affective* OR nervous* OR psychiatric* OR mood* OR emotion* OR mental* AND perfectionis*. To ensure results were not limited to particular study designs, methodological filters were not applied. Additional literature was sought through citation chaining; references of selected articles were examined, and forward searches were completed via the Google Scholar search engine. References of relevant systematic reviews identified during searching were also explored. Searches were updated in April 2020.

Study Selection

Screening was completed independently by two authors (AW and LOR). Relevance was assessed through simultaneous screening of titles and abstracts. Potentially relevant papers were examined in full. Where consensus could not be reached, views of the wider research team were sought. Inclusion was contingent upon: a) publication in English; b) publication in a peer reviewed journal; c) research participants being aged 18 to 65 years with a clinical diagnosis of either CFS, ME, Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS), Post Viral Fatigue Syndrome or Post Viral Syndrome; d) use of validated psychometric measures (or subscales of validated measures) to assess perfectionism and either depression, anxiety or a composite score (emotional distress); and e) reporting of quantitative, cross-sectional data pertaining to the relationship(s) between perfectionism and depression/anxiety/emotional distress. Intervention studies were included if they reported bivariate and/or multivariate analyses of variables pre-intervention; post-intervention data were excluded, as were retrospective reports.

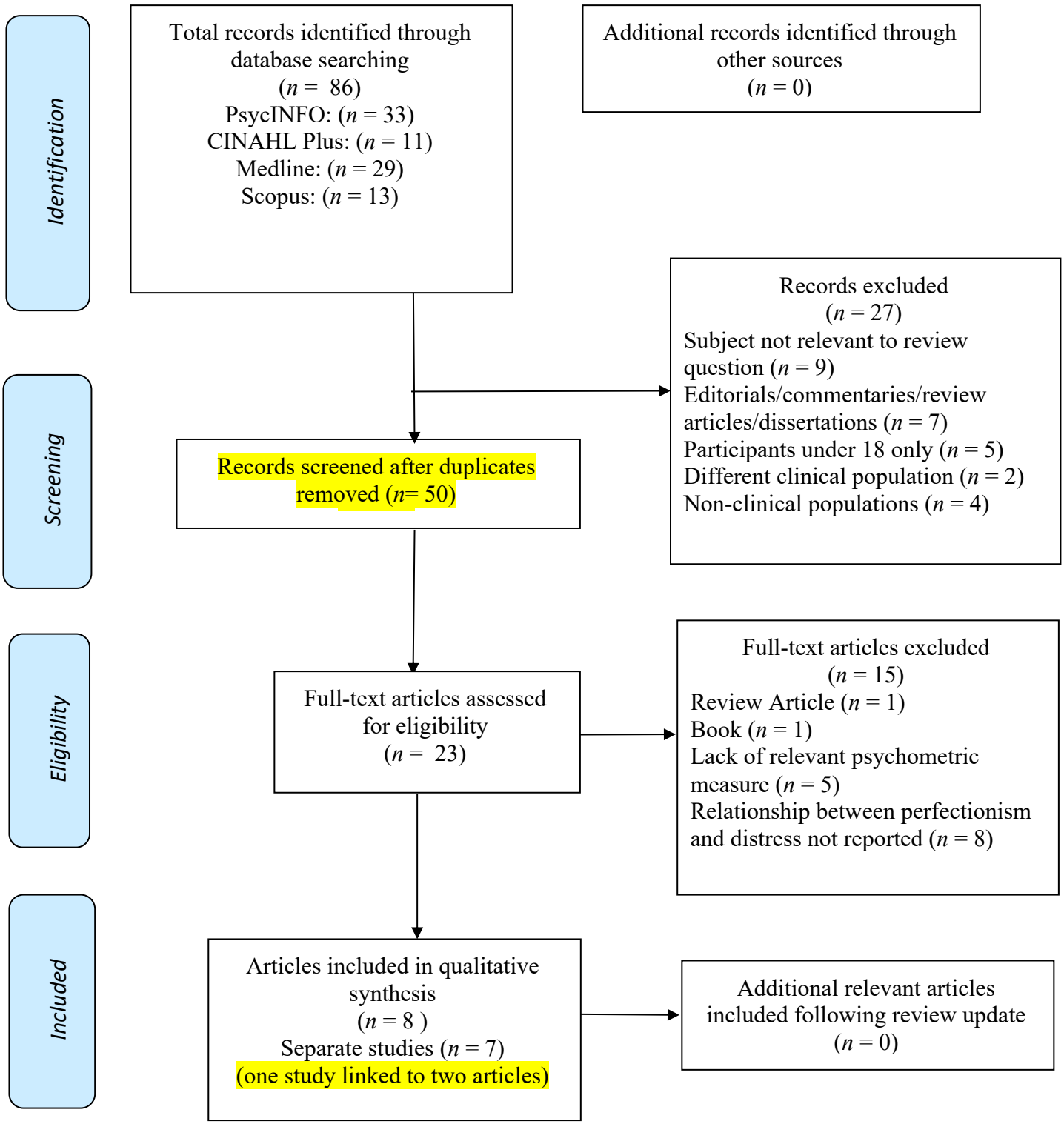

Figure 1.

PRISMA Diagram Summarising the Screening Process for Included Studies

Assessment of Risk of Bias

Included papers were assessed independently by two authors (AW and LOR) for risk of bias using a tool (Appendix C) adapted from the Agency for Healthcare Research and Quality [65, 66]. The tool assesses risk of bias in studies across a range of domains relevant to research with physical health populations. Criteria relating to intervention study follow up data were removed to ensure relevance to this study. Unbiased selection of cohort criteria was adapted to reflect a representative sample of the CFS/ME population. Criteria for cohort description and analysis of confounders were adapted to include CFS/ME specific factors.

Resolution of uncertainty was reached through either consensus or consultation with the wider research team. In line with CRD guidance [63], studies were not excluded where risk of bias was indicated; however, this was considered when interpreting results. Reviewers were not blinded to the authors, institutions, or journals of included studies.

Data Extraction and Analysis

Extraction of relevant clinical, demographic and methodological data was completed by AW and checked for accuracy by a second author (LOR). Where studies included control groups, only data for the CFS/ME population were extracted. Data extracted from linked studies were reported as a single study, listing all relevant publications. Where multiple analyses were reported, data from the following were extracted: a) bivariate analyses examining associations between measures of perfectionism and emotional distress (anxiety and/or depression); and/or b) multivariate analyses, in which the effects of potential confounders on the aforementioned correlations were controlled for. Where necessary, authors were contacted to obtain missing data. Due to the range of psychometric measures and subscales used across a relatively small number of studies, meta-analysis was not possible.

Results

The main characteristics of the included studies [67-74] are detailed in Table 1. An overall sample of 702 participants was reported upon. All studies were conducted in Europe. Two used a longitudinal design [70, 72]; the remainder were cross-sectional. All studies recruited samples of patients using CDC diagnostic criteria [2]. Four studies specified additional criteria to increase diagnostic rigour [70, 71, 73, 74]. Four studies, reported in five papers [67, 68, 69, 71,72], reported mean time since illness onset, which ranged from 36 to 72 months.

Six studies, reported in seven papers, reported on educational attainment [67, 68, 69 70,71,73,74]. Approximately half of the overall sample had completed either secondary or tertiary education, and approximately one third had completed higher education.

Four papers reported mean depression severity [70,71,73,74]; all exceeded minimum thresholds for clinical caseness as measured by either the Beck Depression Inventory [75] (> 9) or the Hospital Anxiety and Depression Scale [76] (> 8); Two papers [67, 69] reported proportion of participants meeting at least minimum clinical cut-offs for depression, ranging between 33-40.1%. A single study [67] reported on the percentage participants meeting clinical cut of scores for anxiety (43%).

Table 1

Characteristics of Studies ***(n = 7)***

Study Characteristics						Participant Characteristics					
Author	**Design**	**Location**	**Sampling method**	**n**	**Female (%)**	**Age, mean (SD) *Range***	**Highest educational attainment (percentage)**	**Exclusion of co-morbid psychiatric diagnoses?**	**Diagnostic /assessment criteria specified**	**Distress Score (SD) *Measure***	**Time since onset in months mean**
Blenkiron et al., 1999 [67]	Cross -sectional	UK	Purposive	40	60	49 (median) *21-66*	*Median years in education since aged 16*: 5	No	CDC[a]	33% met criteria for depression *HADS-D* (8 >) 43%.met criteria for anxiety *HADS-A* (8 >)	36
Kempke et al., 2011 [68 & 69][l]	Cross-sectional	Belgium	Purposive	192	85.4	40.17 (9.43) *19–66*	Secondary/ Tertiary: 49.2 Higher Education: 45.5	n/s	CDC[a]	Depression n/s *BDIc* 40.1% met depression criteria. *HADS-D*[b]	57.36
Kempke et al., 2015 [70]	Longitudinal	Belgium	Purposive	40	100	41.93 (7.99) *28—58*	Secondary/ Tertiary: 51 Higher Education: 43.6	Yes. Exclusions: 'psychiatric diagnoses which may explain fatigue'	CDC[a] Medical evaluation	Depression 8.72 (3.86) *HADS-D*	n/s

Table 1: continued

Luyten et al., 2006 [71]	Cross-sectional	Belgium	Purposive	43	86	39.1 (7.91) *22-58*	Mean: 1.09 [c] (SD .89)	n/s	CDC[a] Biological & Psychological Assessment.	Depression 11.88 (7.95) *BDIc*	39.1
Luyton et al., 2011 [72]	Longitudinal	Belgium	Purposive	57	93	42.19 (8.33) *18-59*	n/s	n/s	CDC[a]	Depression n/s *BDIc*	72.36
Valero et al., 2013 [73]	Cross-sectional	Spain	Purposive	229	91.3	48.21 (8.93) *22-73*	Secondary/ Tertiary: 41.4 Higher Education: 20.2	Yes. Exclusions: 'severe unstable psychiatric disorders' [d]	CDC[a] Medical evaluation. Psychiatric / Psychological assessment.	Depression 10.35 (4.95) *HADS-D*	n/s
Wood & Wessely., 1999 [74]	Cross-sectional	UK	Purposive	101	60.4	36.6 (10.5)	Secondary/ Tertiary: 58.41 Higher Education: 28.71	n/s	CDC[a] UKoc Psychiatric assessment	15.3 BDI 13.6 BDIc	[e]

Note. BDI = Beck Depression Inventory [75]; BDIc = Beck Depression Inventory corrected (items 15, 16 & 17 removed due to symptomatic overlap); CDC = Centre for Disease Control criteria for CFS [2]; HADS-A = Anxiety subscale of Hospital Depression and Anxiety Scale [76]; HADS-D = Depression subscale of Hospital Anxiety and Depression Scale [76]; n/s = not specified; UKoc = UK operational criteria [77].

Data reported to two significant figures where possible.

[a] Centre for Disease Control criteria for CFS [2] specifies the following as exclusions of diagnosis: 'Any past or current diagnosis of major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa; bulimia nervosa';

[b] Clinical cut off not specified.

[c] *5-point scale:* 1=primary; 0=lower secondary; 1=higher secondary; 2=undergraduate; 3=university

[d] 'Severe unstable psychiatric disorders' specified: 'a psychotic episode, a major depressive episode, maniac episode, substance use disorders and anorexia nervosa';

[e] Authors state a median number of months: 3621-58.

[1] linked studies [68 & 69]

Assessment of Risk of Bias

The assessment of risk of bias is shown in Table 2. The main limitations relate to sample size justification and selection, in addition to control of potential confounders in analyses. All studies used the CDC diagnostic criteria [2]; whilst frequently used in research and clinical diagnosis, this arguably captures a larger, more heterogeneous group, with a broader range of symptom severity than captured by more stringent diagnostic criteria [78]. Studies recruited from specialist CFS health services, with most sampling consecutive patients [68, 69, 70,72,73,74]. Whilst increasing rigour regarding diagnosis confirmation, this introduces a selection bias; samples reflect a subset of patients, willing and able to access mainstream health services at a particular time point. Four studies, reported in five papers, recruited from the same hospital-based CFS centre [68 - 72]. Only one study randomly selected participants from a waiting list [67]. Subsequently, generalizability of findings to the wider CFS/ME population is questionable. No study reported a sample size calculation, rendering consideration of statistical power problematic and suggesting potential Type 1 errors. Descriptions of demographics were partial. Four studies [68, 71, 72, 74] used a corrected form of the BDI [75] with items 15, 16 and 17 removed due to symptomatic overlap (BDIc). Two papers partially controlled for cross-sectional confounders when analysing the relationship between perfectionism and depression [69, 71]; however, time since CFS/ME onset, physical and cognitive symptom severity were not accounted for.

Table 2

Assessment of Risk of Bias

Author	Unbiased selection of cohort?	Sample size calculation	Adequate description of cohort	Validated measure of perfectionism	Validated measure of depression and/ anxiety	Recognised diagnostic criteria / medical assessment for CFS	Cross -sectional confounders Controlled for?	Appropriate analyses
Blenkiron et al. [67]	Partially	n/s	Partially	Yes.	Yes.	Yes	No	Partially
Kempke et al. [68][1]	Partially	n/s	Partially	Yes	Yes	Yes	No	Partially
Kempke et al. [69][1]	Partially	n/s	Partially	Yes	Yes	Yes	Partially	Partially
Kempke et al. [70]	Partially	n/s	Partially	Yes	Yes	Yes	No	Partially
Luyten et al. [71]	Partially	n/s	Partially	Yes.	Yes	Yes	Partially	Partially
Luyton et al. [72]	Partially	n/s	Partially	Yes	Yes	Yes	No	Partially
Valero et al. [73]	Partially	n/s	Partially	Yes	Yes	Yes	No	Partially
Wood & Wessely, [74]	Partially	n/s	Partially	Yes	Yes	Yes	No	Partially

Note. n/s = not specified

[1] linked studies [68 & 69]

Assessment of Perfectionism

All studies used self-report measures of perfectionism, most frequently the Frost Multidimensional Perfectionism Scale (MPS-F) [79]. Subscales assess 'concern over mistakes'; 'doubts about actions'; 'personal standards'; 'organisation' (a preference for orderliness and organization); 'parental expectations' and 'parental criticism' (as perceived by the individual); plus a composite score. Two papers [69,73] measured a latent variable of 'maladaptive perfectionism', using the 'concern over mistakes' and 'doubts about actions' subscales [46, 79]. One study [67] used the Multidimensional Perfectionism Scale (MPS) [80], which measures 'self-orientated'; 'other-orientated'; and 'socially prescribed' perfectionism, plus a composite score. Two studies [70, 72] employed the 'self-critical perfectionism' subscale of the Depressive Experiences Questionnaire (DEQ) [81].

Assessment of Depression and Anxiety

All studies assessed depression, using either the HADS or a corrected version of the BDI [75] (Table 3). One study [67] assessed both anxiety and depression, using the HADS. No study used measures specifically designed to assess anxiety of depression in people living with CFS/ME.

Table 3

Measures of Dependent and Outcome Variables

Variable	Measure	Used by	Subscales
Perfectionism	MPS	Blenkiron et al. [67]	Self-orientated; other-orientated; socially prescribed; total perfectionism
	MPS-F	Kempke et al. [68][1]	Concern over mistakes (CM); doubts about actions (DA); personal standards (PS)
			PS = 'adaptive perfectionism'
			CM+DA = 'maladaptive perfectionism'
		Kempke et al. [69][1]	Concern over mistakes (CM); doubts about actions (DA)
			CM+DA = 'maladaptive perfectionism'
		Luyten et al. [71]	Personal standards (PS); concern over mistakes (CM); doubts about actions (DA); organisation (O); parental expectations (PE); parental criticism (PC)
		Valero et al. [73]	CM+DA = 'maladaptive perfectionism'
		Wood & Wessely [74]	Personal standards (PS); concern over mistakes (CM); doubts about actions (DA); organisation (O); parental expectations (PE); parental criticism (PC)
			Total perfectionism: (CM+DA+PS+PE+PC)
	DEQ	Kempke et al. [70]	Self-critical perfectionism (S-CP)
		Luyton et al. [72]	Self-critical perfectionism (S-CP)
Depression	HADS	Blenkiron et al. [67]	HADS-D
		Kempke et al. [69][1]	HADS-D
		Kempke et al. [70]	HADS-D
		Valero et al. [73]	HADS-D
	BDIc	Kempke et al. [68][1]	N/A
		Luyten et al. [71]	N/A
		Luyton et al. [72]	N/A
		Wood & Wessely [74]	N/A
Anxiety	HADS	Blenkiron et al. [67]	HADS-A

Note. BDIc = Beck Depression Inventory [75] corrected (items 15, 16 & 17 removed due to symptomatic overlap); DEQ = Depressive Experiences Questionnaire [81]; HADS = Hospital Anxiety and Depression Scale [76]; HADS-A = Hospital Anxiety and Depression Scale, anxiety subscale; HADS-D = Hospital Anxiety and Depression Scale, depression subscale; MPS = Multidimensional Perfectionism Scale [80]; MPS-F = Frost Multidimensional Perfectionism Questionnaire [79]; N/A = not applicable to study.

[1]linked studies [68 & 69].

Adaptive and Maladaptive Perfectionism

Statistically significant positive associations were evidenced between depression and both 'concern over mistakes' and 'doubts about actions', as well as the latent variable 'maladaptive perfectionism' [68, 69, 71, 73, 74]. Associations between depression and 'doubts about actions' ranged from .46 to .60; associations between depression and 'concern over mistakes' ranged between .35 and .60. When controlling for all perfectionism subscales using the MPS-F, Luyton et al. [71] found 'doubts about actions' was significantly associated with depression severity ($\beta = .47$, $p < .04$). Kempke and colleagues [69] found 'maladaptive perfectionism' was significantly associated with depression ($\beta = .34$, $p < .001$); however, this association was no longer significant when controlling for self-esteem ($\beta = .8$, ns), which fully mediated the relationship between perfectionism and depression. It is important to note that cross sectional data were used for the mediation analysis which means that a causal relationship cannot be assumed. Mixed support was found for the association between depression and 'personal standards' (also termed 'adaptive perfectionism'); the significant moderate associations reported by Kempke and colleagues ($r = .33$, $p < .001$) [68] and Luyton and colleagues ($r = .32$, $p < .05$) [71] were not found by Wood and Wessely ($r = .15$, $p = .10$) [74].

Organisation

Of the two studies that looked at association depression and 'organisation', one found a significant positive correlation [71] ($r = .41$, $p < .01$), whilst the other found no relationship ($r = .02$, $p = .99$) [74]. When controlling for all other factors of perfectionism, Luyton and colleagues [71] found 'organisation' was a significant and positive statistical predictor of depression severity ($\beta = .43$, $p < .01$).

Parental Factors of Perfectionism

Small, non-significant associations were found between depression and 'parental expectations' (r = .18, ns; r = .12, p = .19) [71, 74]. However, the small significant association between depression and 'parental criticism' (r = .18, p = .05) reported by Wood and Wessely [74] was not found by Luyton and colleagues (r = .20, ns) [71].

Self-Critical Perfectionism

Findings regarding the association between depression and 'self-critical perfectionism' were mixed. A small, non-significant association (r =.22, ns) was reported by Kempke and colleagues [70]. However, Luyton and colleagues, [72] found a significant, moderate correlation (r= .48, p< .001).

Self-Orientated; Other-Orientated and Socially Prescribed Perfectionism

The single study [67] assessing anxiety found no significant associations with either 'self-orientated'; 'other-orientated' or 'socially prescribed' perfectionism.

Total Perfectionism

Two studies reported a composite perfectionism score: one using the MPS [67] and one using the MPS-F [74]. The former reported no significant association between total perfectionism and either depression (r = .07, ns) or anxiety (r = -.01, ns) [67]. The latter [74] reported a significant association with depression (r =.37, p < .001), but excluded the 'organisation' subscale.

Table 4.

Main Findings – Associations Between Perfectionism and Depression and Anxiety.

Perfectionism Type	Authors	Method of Assessing Perfectionism (Subscales)	Statistical Analyses	Effect Size: Depression (p)	Effect Size: Anxiety (p)
'Maladaptive'	Kempke et al. [69][1]	MPS-F (CM; DA)	Pearson's correlation	*r* =*.48*** *(p<.001)*	N/A
	Valero et al. [73]			*r* = .42** *(NR)*	N/A
'Self-critical'	Luyton et al. [72]	DEQ (SC-P)		*r* = .48*** *(p<.001)*	N/A
	Kempke et al., [70]			*r* =.22 *(ns, NR)*	N/A
Total	Blenkiron et al. [67]	MPS		*r* = .07 *(ns, NR)*	*r* = -.01 *(ns, NR)*
	Wood & Wessely [74]	MPS-F (CM, DA, PS, PE, PC)		*r* =.37*** *(p<.001)*	N/A
Self-orientated	Blenkiron et al. [67]	MPS (SO)	Spearman's correlation	*r* = -.06 *(ns, NR)*	*r* = -.69 *(ns, NR)*
Other-orientated		MPS (OO)		*r* = -.13 *(ns, NR)*	*r* = -.22 *(ns, NR)*
Socially prescribed		MPS (SP)		*r* = .23 *(ns, NR)*	*r* = .06 *(ns, NR)*
'Adaptive' Personal Standards	Kempke et al. [68] [1]	MPS-F (PS)	Pearson's correlation	*r* =.33*** *(p<.001)*	N/A
	Luyton et al. [71]			*r* = .32* *(NR)*	N/A
	Wood & Wessely [74]			*r* = .15 *(p = .10)*	N/A
Concern over Mistakes	Kempke et al. [68] [1]	MPS-F (CM)		*r* = .60*** *(p<.001)*	N/A
	Kempke et al. [69] [1]			*r* = .40*** *(p<.001)*	N/A
	Luyton et al. [71]			*r* = .43** *(NR)*	N/A
	Wood & Wessely [74]			*r* = .35*** *(p<.001)*	N/A
Doubts about Actions	Kempke et al. [68]1	MPS-F(DA)		*r* =.60*** *(p<.001)*	N/A
	Kempke et al. [69]1			*r* =.53*** *(p<.001)*	N/A
	Luyton et al. [71]			*r* =.51*** *(p<.001)*	N/A
	Wood & Wessely [74]			*r* = .46*** *(p<.001)*	N/A

Table 4. *continued*

Organisation	Luyton et al. [71]	MPS-F (O)	*r =.41*** *(NR)*	N/A
	Wood & Wessely [74]		*r = .02 (p = .99)*	N/A
Parental Expectations	Luyton et al. [71]	MPS-F (PE)	*r* = .18 *(ns, NR)*	N/A
	Wood & Wessely [74]		*r* = .12 *(p = .19)*	N/A
Parental Criticism	Luyton et al. [71]	MPS-F (PC)	*r= .20 (ns, NR)*	N/A
	Wood & Wessely [74]		*r* = .18* *(p = .05)*	N/A

Note. CM = concern over mistakes; DA =doubts about actions; DEQ = Depressive Experiences Questionnaire [81]; MPS = Multidimensional Perfectionism Scale [80]; MPS-F= Frost Multidimensional Perfectionism Questionnaire [79]; N/A = not applicable to study; NR = not reported; ns = non-significant; O = organisation; OO = other-orientated; PC = parental criticism; PE = parental expectations; PS = personal standards; S-CP = self-critical perfectionism; SEM = structured equation modelling; SO = self-orientated; SP= socially prescribed.

* $p < .05$; ** $p < .01$; *** $p < .001$. *Exact p values reported where stated in publication.*

[1]Linked studies [68 & 69].

[2]MPS-F minus 'organisation' subscale.

Table 5

Main Findings from Multi-Variate Analysis: Depression

Author	**Analysis**	**Variables**			**Significant findings**
		Perfectionism (factor) ***Measure***	**Psycho-social**	**Non-Psycho-Social**	
Kempke et al. [69][1]	RA	MAL (CM, DA)	Self-esteem	None	None
Luyten et al. [71]	HMRA	PS; CM; DA; O: PE; PC	None	None	Organisation: β = .43, *p*< .01 Doubts about Actions: β = 47., *p*< .04

Note. CM = concern over mistakes; DA= doubts about actions; HMRA = hierarchical multiple regression analysis; MAL = maladaptive perfectionism; O = organization; PC = parental criticism; PE parental expectations; RA: regression analysis.

[1] linked study [68 & 69].

Discussion

This systematic review examined the relationship between perfectionism and emotional distress (depression and/or anxiety) in people living with CFS/ME. Systematic searches revealed a paucity of data regarding anxiety, as well as heterogeneity in measures of both depression and perfectionism. Results therefore primarily focus on associations between depression and specific aspects of perfectionism in people living with CFS/ME.

When treated as a unidimensional construct, perfectionism was not consistently associated with depression. However, 'maladaptive perfectionism', and the composite subscales of 'doubts about actions' and 'concern over mistakes' were consistently associated with depression [68, 69, 71, 73, 74]. Nevertheless, only two studies [69, 71] controlled for cross-sectional confounders; one of these being other factors of perfectionism [71]. Subsequently, it is not known whether the relationship between maladaptive perfectionism and depression would hold once other variables are controlled. A single study [69] found 'maladaptive perfectionism' was no longer a significant statistical predictor of depression severity, when controlling for self-esteem. However, greater consideration of the relationships between distress and both pre-and post-morbid perfectionism and self-esteem is needed.

Findings regarding the association between depression and other factors of perfectionism were mixed. This likely reflects the smaller number of studies eligible for inclusion in this review. However, in the case of adaptive perfectionism, this is consistent with psychological theory and existing literature [49]; 'adaptive perfectionism' may confer some psychological benefits [46, 82]. Mixed findings regarding 'adaptive perfectionism' may be considered alongside findings by Deary and Chalder [60], who concluded 'adaptive perfectionism' may cease to be adaptive in People living with CFS/ME, due to its correlation

with ‘maladaptive perfectionism’; striving to achieve standards may in fact trigger self-doubt, self-criticism and worry [60, 83].

Methodological Limitations and Implications for Future Research

Analysis of cross-sectional data from seven studies offers preliminary evidence that ‘maladaptive perfectionism’ is associated with depression in people living with CFS/ME. Whilst the hypothesized causal role of ‘maladaptive perfectionism’ is grounded in theory and previous research [37, 39, 46, 54], firm conclusions cannot be drawn regarding generalisability or causality without further research.

Divergent findings may have resulted in part, from differential measurements of both perfectionism and distress. At the same time, all primary models of trait perfectionism and the related psychometric measures were not represented in the selected studies. Notably absent was the Almost Perfect Scale-Revised [84], which measures ‘high standards’, ‘order’, and ‘discrepancy’. Whilst the former two subscales overlap with factors measured by the MPS and MPS-F, the unique factor of ‘discrepancy’ refers to the disparity between standards and the degree to which these are perceived to be achieved [84]. This is likely to be relevant in the relationship with depression/anxiety; people living with CFS/ME may be particularly vulnerable due to the inability to meet pre-morbid standards. Measures which encompass multiple subscales [85] may enable a broader focus in future research, whilst maintaining methodological consistency.

Included studies did not adequately consider or test a range of mechanisms through which perfectionism and distress may be linked. Similarly, the search identified studies measuring perfectionism at the trait level only. Future studies may also usefully examine the potential mediating role of perfectionistic cognitions [86 - 89].

The inclusion of peer reviewed articles only sought to ensure quality. However, this may have introduced a publication bias [90]. Language, selection or cultural bias may also have been introduced by the inclusion of only articles published in English. Similarly, all studies were conducted in Europe.

Participants were predominantly females in their thirties and forties, reflecting what is known about the demographics of CFS/ME [15, 16]. Generalisability is nevertheless unclear, as the sample consisted solely of people in receipt of services and diagnosed using the CDC criteria. Whilst the single diagnostic criteria (CDC) facilitated direct comparison across studies, this arguably captured a heterogenous group [78]. Further research may usefully examine the relationship between perfectionism and emotional distress in relation to categories of CFS/ME symptom severity.

Further research is needed which specifically focusses on the associations between perfectionism and emotional distress in CFS/ME. Examining the interplay between 'maladaptive perfectionism', fatigue and both depression and anxiety would enhance clinical understanding. Further insight may be gained through examining psychological mechanisms through which perfectionism may affect levels of depression and anxiety. Longitudinal designs would facilitate greater confidence in concluding causality. Prospective studies may usefully track patient groups at risk of developing CFS/ME, such as those experiencing glandular fever [61]. This would enable analysis of pre- and post-morbid perfectionism and emotional distress. Samples including patients both engaged and no longer engaged in mainstream health services may be more representative of the CFS/ME population. Consistency of measures would further enable development of the evidence base. In researching 'concern over mistakes' and 'doubts about actions', methodological rigour may be enhanced through statistically controlling for cognitive symptoms of CFS/ME [91], which may interact with these factors of perfectionism.

Theoretical and Clinical Implications

Divergent findings regarding the relationship between depression and different aspects of perfectionism corroborated its status as a multifactorial construct [36]; treatment as a unidimensional concept would risk masking the differential impact of adaptive and maladaptive factors upon depression and/or anxiety.

A single study found self-esteem mediated the relationship between maladaptive perfectionism and depression. Whilst further research is needed to corroborate this outcome, this is consistent with psychological theory; perceived failure to meet standards of an ideal self may increase depression vulnerability, via self-esteem being overly dependent upon productivity and accomplishment [54]; This is consistent with evidence of low self-esteem in people living with CFS/ME [57], and indicates the potential relevance of 'discrepancy' [84] as a factor of perfectionism.

'Maladaptive perfectionism' was consistently associated with depression in CFS/ME, indicating these provisional findings could have implications for further research. Clinical recommendations are based on prospective findings from cross-sectional research, which require corroboration from further studies.

Rather than targeting high personal standards per se, therapeutic techniques addressing 'concern over mistakes' and 'doubts about actions' may be efficacious in reducing depression. This may reduce the somatic overlay, which is likely to exacerbate fatigue. Clinical consideration would be required on an individual basis, regarding the relationship between 'doubts about actions', 'concern over mistakes' and the level of cognitive symptoms experienced [91]; difficulties with memory and concentration may further increase such perfectionistic concerns, which may drive checking behaviours and increased energy expenditure. This may push people beyond their 'energy envelope' [92].

Targeting ‘maladaptive perfectionism’ in management programmes may facilitate more adaptive coping strategies and adjustment to living with chronic illness. This may potentially reduce the risk of ‘boom and bust’ activity patterns [93] and checking behaviours, triggered by a desire to meet unrealistic, self-imposed and possibly pre-morbid standards. This may be important for relapse prevention, regarding both CFS and co-morbid depression. Where psychometric measures indicate relevance, psychoeducation may facilitate understanding of the advantages and disadvantages of perfectionism and give a focus for change. This may be particularly important for those either retaining or returning to some degree of employment or educational activity; perfectionistic concerns are likely to be triggered more easily in these environments.

Conclusions

To our knowledge, this is the first systematic review to examine the relationship between different aspects of perfectionism and emotional distress in people living with CFS/ME. Findings suggest the association between perfectionism and anxiety is an under-researched area in this patient group. However, maladaptive perfectionism was consistently found to be associated with depression. It would be clinically meaningful to establish whether there are links between maladaptive perfectionism, fatigue and both depression and anxiety. Understanding the dynamic relationships between these variables may ultimately contribute to the development of efficacious therapeutic interventions, as part of a 'living well with chronic illness' approach.

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Chapter 2: Empirical Paper

Comorbid Depression and Anxiety in Chronic Fatigue Syndrome: The Role of Metacognition

Running head: Metacognition, depression, and anxiety in CFS

Comorbid Depression and Anxiety in Chronic Fatigue Syndrome: The Role of Metacognition

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Abstract

Objectives: Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) frequently experience comorbid depression and anxiety. The transdiagnostic Self-Regulatory Executive Function (S-REF) model proposes that metacognitive beliefs activate and maintain depression and anxiety, both directly and indirectly by driving a cognitive attentional syndrome (CAS). However, the fit of the S-REF model to understanding depression and anxiety in patients with CFS/ME has not yet been examined. **Design**: A cross-sectional design using multiple self-report measures. **Method**: Adults with a self-confirmed diagnosis of CFS/ME (N=235) completed measures of depression, anxiety, fatigue, metacognitive beliefs and use of the CAS. Data were analysed using hierarchical regression modelling and mediation analyses. **Results**: When controlling for demographic and clinical variables, metacognitive beliefs accounted for an additional 8.2 % of the variance in depression and an additional 14.5 % of the variance in anxiety. Specific metacognitive beliefs domains made independent contributions to the final models for both depression and anxiety. The relationship between positive metacognitive beliefs and depression was fully mediated by the CAS. Relationships between negative metacognitive beliefs and both depression and anxiety, and positive metacognitive beliefs and anxiety were partially mediated by the CAS. **Conclusions**: Metacognitive beliefs are both directly and indirectly associated with depression and anxiety in people living with CFS/ME. If corroborated by longitudinal evidence, future studies should test the clinical impact of targeting metacognitive beliefs and processes upon depression and anxiety.

Keywords: Chronic Fatigue Syndrome; Myalgic Encephalomyelitis; Depression; Anxiety; Metacognitive Beliefs; Cognitive Attentional Syndrome.

Summary of Relevant Literature

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is a complex, heterogenous clinical presentation (Martín-Martínez & Martín-Martínez, 2019) with considerable debate surrounding its aetiology, diagnostic nomenclature and treatment (Brurberg et al., 2014; Jason et al., 2014). Prevalence is estimated to be between 0.2% and 2.6% (Nacul et al., 2011; Reyes et al., 2003), dependent upon diagnostic criteria (Johnston et al., 2013). The predominant symptom is persistent, medically unexplained fatigue of new onset, which is unalleviated by rest, exacerbated by mental or physical activity, and which causes significant impairment (Fukuda et al., 1994). A multisystemic condition is indicated by the broad range of additional symptoms, including endocrinological, immunological, neurological and cognitive dysfunction (Cortes Rivera et al., 2019; Glassford, 2017). The latter, subjectively experienced as exaggerated mental fatigue, is proposed to be a dynamic interplay between cognitive, physiological, and perceptual factors (Ocon, 2013).

Significant variability exists in symptom presentation and severity (Zaturenskaya et al., 2009), with the latter categorized as either mild, moderate, severe or very severe (Cox & Findley, 1998; 2000; National Institute for Health and Care Excellence, [NICE, 2007]). Those most severely affected are confined to bed and become highly sensitive to light and sound (Strassheim et al., 2017). In mild cases, people are able to maintain pre-morbid activities such as employment, despite experiencing symptoms; however, this often comes at the expense of leisure and social time (Cox & Findley, 1998; 2000), impacting significantly upon quality of life and emotional wellbeing. Prognosis estimates vary (Cortes Rivera et al., 2019), reflecting the heterogeneity of the condition, as well as differential criteria for recovery (Cairns & Hotopf, 2005). Symptom improvement is more common than full recovery, with estimates of the latter being less than 10% (Cairns & Hotopf, 2005; Vercoulen et al., 1996).

People living with CFS/ME frequently experience comorbid depression and anxiety (Larkin & Martin, 2017), with prevalence estimates of 36%-70% (Fuller-Thomson & Nimigon, 2008; Iwase et al., 2008) and 32%-57% (White et al., 2011; Fischler et al., 1997) respectively. By comparison, point prevalence for common mental health difficulties is approximately 17% of the general population, with 3.3% reporting depression, 5.9% reporting generalized anxiety and 7.8% reporting mixed anxiety and depression (McManus et al., 2016). However, levels of depression and anxiety do not linearly increase with CFS symptom severity (Janal, Ciccone, & Natelson, 2006), indicating that other factors may mediate the relationship between fatigue and depression and anxiety.

Comorbid mental health difficulties are associated with poorer prognosis (Cairns & Hotopf 2005) and depression is an important predictor of CFS treatment outcome (Kempke et al., 2010). However, current psychological interventions primarily seek to reduce fatigue levels and increase physical functioning (White et al., 2011), which can alleviate anxiety and depression as a secondary outcome (Price et al., 2008).

Recommended in NICE Guidelines (2007) for CFS/ME, traditional Cognitive Behavioural Therapy (CBT) focusses on restructuring 'dysfunctional illness perceptions' and beliefs, and reversing behavioural avoidance (Geraghty et al., 2019). Critics argue that the model underpinning CBT discounts the lived experience of patients, as well as the growing evidence of organic pathophysiology in CFS/ME (Geraghty et al., 2019). NICE guidelines are under review following concerns regarding the limited efficacy and potential harm of CBT, including increased distress in some cases (Laws, 2017; Vink & Vink-Niese, 2019). The ME Association (2015) proposes the role of psychological therapy should be limited to treating co-morbid issues such as depression and anxiety, and to promote effective coping with the impact of physical symptoms. Greater understanding of psychological mechanisms underpinning depression and anxiety are therefore needed to facilitate the development of

effective and acceptable therapeutic interventions; given the controversy, acceptability to the patient population is vital when considering potential treatment modalities, due to implications for uptake and adherence (Price et al., 2008).

Whilst CBT could focus specifically on alleviating co-morbid depression and anxiety, Metacognitive Therapy (MCT; Wells, 2009) may be more appropriate for a 'living well with chronic illness approach'. People with CFS/ME frequently experience CBT as invalidating due to its focus on illness perceptions and beliefs (Geraghty & Esmail, 2016; ME Association, 2015). Within the context of physical health, 'negative thoughts' may well reflect accurate and understandable fears regarding the illness and its' impact (Cherry et al., 2019) and, in the case of CFS/ME, additional concerns may include diagnostic and prognostic uncertainty (Ware, 1992; Whitehead, 2006). Rather than questioning the validity of negative thoughts themselves, MCT targets the psychological process through which patients engage with these thoughts, namely worry and rumination.

MCT is an effective treatment for a range of affective and anxiety disorders (Normann et al., 2014), in addition to emotional distress within physical health populations (Elzami et al., 2015; Fisher et al., 2019; Mirhosseini et al., 2015). This suggests the potential utility of MCT in treating co-morbid depression and anxiety in CFS/ME. However, prior to evaluating the intervention, it is necessary to test predictions of the underlying theory in this patient group.

MCT is based upon the trans-diagnostic Self-Regulatory Executive Function (S-REF) model (Wells & Matthews 1994). According to this model, prolonged distress does not result from thought content or CFS/ME-related appraisals per se, but rather metacognitive beliefs or 'thinking about thinking'. Metacognitive beliefs drive unhelpful thought processes and responses, termed the cognitive-attentional syndrome (CAS; Wells & Matthews 1994). The CAS consists of perseverative thinking, attentional focus upon threat, and maladaptive

cognitive and behavioural coping strategies, such as thought suppression and reassurance seeking. These patterns arise in response to perceived cognitive, behavioural, or emotional triggers, all of which may relate to physical illness.

Two types of metacognitive belief about worry/rumination are theorised to be of particular significance in activation and maintenance of the CAS via differential pathways (Wells & Matthews, 1994); positive metacognitive beliefs (PMCBs) about the usefulness of worry, such as 'worrying helps me cope', and negative metacognitive beliefs (NMCBs) about the uncontrollability and danger of worry, such as 'when I start worrying, I cannot stop'. PMCBs indirectly cause distress by promoting the use of worry/rumination as coping strategies. NMCBs about the uncontrollability and dangerousness of worry cause distress both directly and indirectly. This is because they are, themselves, distressing and lead to unhelpful cognitive self-regulation patterns, such as thought suppression and avoidance. Furthermore, efforts to control worry may be deemed futile where it is conceived as uncontrollable. Other metacognitive beliefs theorised to contribute to activation and maintenance of the CAS include cognitive self-consciousness, need to control thoughts, and lack of cognitive confidence. MCT aims to interrupt the CAS and modify metacognitive beliefs (Wells, 2009; 2013).

Metacognitive processes are implicated in a wide range of psychological disorders (Wells, 2013). Preliminary evidence indicates the role of metacognitive processes in the emotional distress experienced by physical health populations including cancer (Cook et al., 2015; Fisher et al., 2018) diabetes (Purewal & Fisher, 2018), epilepsy (Fisher, Cook, & Noble, 2016) multiple sclerosis (Heffer-Rahn & Fisher, 2018) and Parkinson's disease (Allott et al., 2005; Brown & Fernie, 2015; Fernie et al., 2015).

Metacognitive processes are activated in response to physical symptoms in people with CFS/ME (Maher-Edwards et al., 2012). These processes include attentional focus on

health-related threat stimuli (Hou et al., 2008), somatic information processing (Moss-Morris & Petrie, 2003), and high levels of worry (Aggarwal et al., 2006). Research has primarily focussed upon the role of metacognitive processes in maintaining physical symptoms (Maher-Edwards et al., 2011; Maher-Edwards et al., 2012). However, it is acknowledged that these processes are also likely to lead to an increase in negative affect (Maher-Edwards et al., 2012; Sohl & Friedberg, 2008).

Despite preliminary evidence indicating associations between metacognitive beliefs and depression/anxiety in people with CFS (Maher-Edwards et al., 2011), this relationship has not been investigated whilst controlling for demographic characteristics and symptom severity. Furthermore, to our knowledge, there is no existing research regarding whether the CAS mediates the relationship between metacognitive beliefs and distress in people with CFS/ME. This study therefore investigates the relationships between metacognitive beliefs, the CAS and anxiety and depression in people with CFS/ME. Specifically, we hypothesise that:

1. Symptom severity (fatigue) will be positively correlated with depression and anxiety.
2. Metacognitive beliefs will be positively correlated with depression, anxiety and fatigue.
3. Metacognitive beliefs will account for a significant proportion of the variance in depression and anxiety, after controlling for fatigue and demographic variables.
4. The relationship between metacognitive beliefs and both depression and anxiety will be mediated by the CAS.

Method

Design

The study used a cross-sectional design, with data collected using multiple self-report measures.

Participants

Participants were 235 people from the United Kingdom who met the following criteria: i) a self-confirmed clinical diagnosis of CFS/ME; ii) aged between 18 and 75 years; and iii) the ability to understand written English.

Procedure

The study was sponsored by the University of Liverpool (Appendices D & E) and ethical approval was granted by the Heath Research Authority (IRAS reference: 253333, Appendix F). Participants were recruited from three specialist CFS/ME NHS clinics in the United Kingdom (n = 16) and online via CFS/ME support groups and related social media pages (n = 219). In respect of recruitment from the NHS, eligible patients were approached by clinical staff during routine appointments or groups. Posters (Appendix G) and consent to contact forms (Appendix H) were also placed in clinics. For online recruitment, advertisements (Appendix I) were placed on consenting CFS/ME support group websites. Snowball sampling was facilitated whereby participants were able to share the online link via social media. Interested individuals were invited to complete an anonymous online survey via the Qualtrics platform. This included the participant information sheet (Appendix J), the consent form (Appendix K) and self-confirmation of having received a clinical diagnosis of CFS/ME (Appendix L). Alternatively, paper surveys were made available upon request. Participants completed measures assessing demographic characteristics, fatigue, depression,

anxiety, and metacognitive beliefs and processes (Appendices L-Q). Upon completion of the measures and reading the electronic debriefing (Appendix R), each participant was given the option of entering a prize draw to potentially win one of ten £15 retail vouchers.

Measures

Descriptor Variables

Demographic data, including age, gender and time since onset of CFS/ME symptoms, were collected using a questionnaire designed for this study (Appendix L). Due to overlap in symptoms and high prevalence of co-morbidities (Aaron et al., 2001; Petersen et al., 2020) additional clinical information was gathered regarding the following self-confirmed diagnoses: depression, fibromyalgia, chronic pain syndrome and irritable bowel syndrome.

Dependent Variable

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983; Appendices M & N) assessed depression, anxiety, and a composite score of emotional distress (HADS-t). The HADS comprises 14 statements about symptoms experienced during the past week. Each statement is scored on a 4-point scale (with anchor points of 0 = *"not at all"* to 3 = *"very often"*). Responses are summed to produce two subscale scores (anxiety and depression) and a composite score. The maximum total score for each subscale is 21. Severity is categorized as mild (8-10); moderate (11-14) and severe (15-21), (Stern, 2014). Caseness of both depression and anxiety in the present sample was defined by a score of eight or more (Olssøn et al., 2005). The HADS is widely used with physical health populations (Bjelland et al., 2002). The HADS demonstrates good internal consistency for patients with CFS/ME regarding the composite score ($\alpha = .87$), depression ($\alpha = .79$) and anxiety ($\alpha = .87$), (McCue et al., 2006). High levels of internal consistency were indicated for this sample regarding the composite score ($\alpha = .92$), depression ($\alpha = .85$), and anxiety ($\alpha = .91$).

Independent Variables

The CFQ 11, an 11-item version of the Chalder Fatigue Scale (Cella & Chalder, 2010; Chalder et al., 1993; Appendix O) assessed fatigue severity. The shorter version of the scale was employed to reduce unnecessary participant burden. The CFQ-11 has two components (physical and mental fatigue). Questions relate to experiences of feeling tired, weak or lacking in energy during the past month. Responses can be scored on a 4-point Likert-scale (anchor points of 0 = *"less than usual"* to 3 = *"much more than usual"*), or bimodally (with columns scoring 0,0,1,1). Bimodal scoring effectively discriminates between CFS sufferers and the general population, with a score of 4 or more indicating clinical caseness (Cella & Chalder, 2010). Mean bimodal scores of 9.14 (SD 2.73) and 3.27 (SD 3.21) are reported for people living with CFS/ME and community samples respectively (Cella & Chalder, 2010). The CFQ 11 has good reliability CFS/ME patient groups (Morriss et al., 1998). Good internal consistency was indicated in this sample ($\alpha = .92$)

The Metacognitions Questionnaire-30 (MCQ-30; Wells & Cartwright-Hatton, 2004; Appendix P) assessed metacognitive beliefs. Subscales of the MCQ-30 measure five metacognitive belief domains: 1) positive beliefs about worry, measuring the perceived usefulness of perseverative thinking; 2) negative beliefs about the uncontrollability and danger of worry, measuring the extent to which perseverative thinking is experienced as uncontrollable and dangerous; 3) lack of cognitive confidence, measuring confidence in memory and attention; 4) the need to control thoughts, measuring beliefs that certain types of thought should be suppressed; and 5) cognitive self-consciousness, assessing tendencies towards thought monitoring and focusing attention inwards. Items are scored from 1 to 4 (anchor points of 1 = *"do not agree"* to 4 = *"agree very much*"). The MCQ-30 demonstrates good internal consistency ($\alpha = .81$ to $\alpha = .92$) in patients with CFS/ME (Maher-Edwards et

al., 2011); the internal consistency for individual subscales in the current study ranged from α = .82 to α = .92.

Mediator Variable

The Cognitive Attentional Syndrome-10 (CAS-10; Wells, 2009; Appendix Q), a 10 item self-report questionnaire, assessed the key aspects of the CAS (worry/rumination, threat monitoring and coping behaviours). Participants are asked to rate the degree to which they have used coping strategies including perseverative thinking during the previous week. Responses are scaled from 0%-100%. Items 1–6 assess perseverative thinking, threat monitoring (e.g. attentional focus on symptoms, thoughts and bodily checking) and unhelpful coping responses (e.g. avoidance and thought suppression). Items 7-10 duplicate items in the MCQ-30 and were therefore disregarded. Good levels of internal consistency were indicated in this sample (α = .87).

Statistical Analysis

Intercorrelations between predictor variables (age, fatigue, time since CFS onset, metacognitive beliefs and the CAS) were tested with parametric and non-parametric methods, as not all scales were normally distributed (Appendix S).

Two multiple hierarchical regressions were used to test whether metacognitive beliefs explained a significant proportion of variance in anxiety (HADS-A) and depression (HADS-D), after controlling for demographic and clinical variables, including level of fatigue. Multicollinearity and tolerance statistics were inspected for all variables (cut offs: variable inflation factor < 10, tolerance > 0.2, Belsley et al., 2005).

The order of entry into the regression was guided by methodological precedence, as well as the theory underpinning the hypotheses. Step one controlled for demographic variables (gender and age); Step 2 controlled for time since onset and co-morbidity with

listed health conditions; Step 3 controlled for level of fatigue; Step 4 controlled for the CAS; Step 5 controlled for metacognitive beliefs. Assumptions of linearity and homoscedasticity were assessed through examining probability plots and scatterplots (Appendix T). Histograms of standardized residual errors were inspected for normal distribution (Appendix T). Due to potential statistical discrepancies between original and log-transformed data (Feng et al., 2014), bootstrapping with 5000 samples was used to adjust for bias and skewness in non-normally distributed variables. Bias-corrected bootstraps give a robust estimation of confidence intervals. Cook's distances were examined for influential cases.

Mediation was used to test for direct and indirect effects of metacognitive beliefs on both depression and anxiety, as predicted by the S-REF model. Four mediation analyses were conducted to test the hypothesized relationships between positive and negative metacognitive beliefs, the CAS, and the independent variables anxiety (HADS-A) and depression (HADS-D). The models examined whether the relationship between these metacognitive beliefs and depression/anxiety operated indirectly via the CAS. Clinical variables relevant to the hypotheses were controlled for, as were those making significant independent contributions in the final regression models. The following criteria were satisfied for conducting mediation analysis: all entered variables were significantly correlated; the models were based upon research indicating the potential role of metacognitive beliefs in causing emotional distress (Wells, 2013); and the associations between emotional distress and metacognitive beliefs were either eliminated or reduced when introducing the CAS (Kraemer et al., 2002). Analyses were completed using SPSS version 25 and the Hayes PROCESS macros (Hayes & Preacher, 2014). Bootstrapping with 5000 samples was used.

Power Calculation

Assuming a medium effect size of .15, 95% power and an alpha of .05 to adjust for multiple regressions, power analysis indicated a minimum of 172 participants were required to power the most complex planned analysis – a multiple regression with 10 predictor variables (1) age; 2) time since initial onset of CFS/ME symptoms; 3) comorbidity with either: fibromyalgia, chronic pain syndrome or IBS; 4) symptom severity (level of fatigue); 5) positive beliefs about worry; 6) negative beliefs about thoughts concerning uncontrollability and danger; 7) lack of cognitive confidence; 8) beliefs about the need to control thoughts; 9) cognitive self-consciousness; 10) the CAS.

Results

Sample Characteristics

Table 1 displays sample characteristics. Of the total sample, 91.91% were female with a mean age of 43.78 years. Gender differences in key variables were examined using Mann Whitney and independent t-tests. No gender differences were found in respect of depression (t (233) = .744, p = .458), anxiety (t (233) = 1.891, p = .060), or fatigue (U = 2370, p = .261).

Of the 235 participants, 220 met the clinical cut off for CFS/ME caseness using the CFQ-11 (Cella & Chalder, 2010). 163 participants reported mean levels of fatigue exceeding that reported for people with a CFS/ME diagnosis (Cella & Chalder, 2010). Common comorbid physical health conditions were reported by 151 participants (64.26 %) with the most common being IBS (43.40 %). There were statistically significant differences in mean HADS-D and HADS-A scores between participants who reported at least one listed physical co-morbidity, and those who did not (t (233) = 2.641, p = .009; t (233) = 5.508 , p < .001). In both cases, mean scores were higher in those reporting listed physical co-morbidities. Similar

differences were found in respect of the CAS (t (233) = 4.704, $p < .001$) and the MCQ-30 (t (233) = 5.174, $p < .001$).

Clinically diagnosed depression was reported by 97 participants, (41.28%); however, HADS scores indicated 68.51% met the clinical threshold. HADS depression or anxiety casesness increased comorbidity of at least one listed condition or more to 186 participants (79.14%). The greatest proportion of depression cases were indicated to be mild-moderate (39.13 % and 36.65 % respectively). Nearly a quarter of cases (24.22 %) were indicated to be severe. The clinical threshold for anxiety was met by 155 participants (65.96%) with the greatest proportion of cases being moderate-severe (42.58% and 39.35 % respectively). The threshold for co-morbid depression and anxiety was met by 133 participants (56.60%).

Table 1.

Sample Characteristics (N = 235)

Variable	N (%) or Mean (SD)
Demographic variables	
Female	216 (91.91%)
Male	19 (8.09%)
Age in years	43.78 (SD 12.72)
Clinical Variables	
Time since CFS/ME symptom onset (years)	13.22 (9.55)
Self-reported dx of depression	97 (41.28%)
Self-reported dx of fibromyalgia	83 (35.32%)
Self-reported dx of chronic pain syndrome	45 (19.15%)
Self-reported dx of irritable bowel syndrome	102 (43.40 %)
Self-reported dx of two or more listed physical health comorbidities	151 (64.26 %)
HADS comorbid Depression and Anxiety	133 (56.60%)
HADS caseness for Depression (> 8)	161 (68.51%)
HADS caseness for Anxiety (> 8)	155 (65.96%)
HADS-D	9.62 (SD 4.76)
HADS-A	10.31 (SD 5.99)
HADS-t	19.93 (SD 9.39)
CFQ-11	10.00 (SD 2.37)

Note: CF-S = Chalder Fatigue Scale; dx = diagnosis; HADS-A = Hospital Anxiety and Depression Scale, anxiety subscale; HADS-D = depression subscale; HADS-t = composite score of depression and anxiety.

Correlations and Descriptive Statistics

Intercorrelations are displayed in Table 2. Consistent with hypothesis 1, CFQ-11 scores were significantly positively correlated with HADS-A, HADS-D and HADS-t scores (r = .275 to .330, p < .001). Consistent with hypothesis 2, all MCQ30 subscales were significantly positively correlated with HADS-A, HADS-D and HADS-t scores (r =.312 to .813, p < .001) as well as CFQ-11 scores (r =.165, p = .011 to .432, p < .001). All MCQ30 subscales were significantly positively correlated with CAS-10 scores (r =.442 to .732, p < .001). Significant positive correlations were found between CAS-10 and HADS-A, HADS-D and HADS-t scores (r =.643 to .773, p < .001). CFQ-11 and CAS-10 scores were moderately correlated (r =.311, p < .001).

Table 2.
Intercorrelations Between Independent Variables, Mediator Variable and Depression and Anxiety

	2	***3***	**4**	**5**	**6**	**7**	***8***	***9***	**10**	**11**	***12***
1.Time Since Onset	*.349***	*-.293***	*-.132**	*-.087*	*-.204***	*-.146**	*-.150**	*-.070*	*-.197***	*-.150**	*.349****
2. Age		*-.077*	-.069	-.171**	.063	-.177**	*-.226****	*-.234****	0.028	-.176**	*-.229****
3.Fatigue (CFQ-11)			*.330****	*.275****	*.324****	*.311****	*.165 **	*.193 **	*.432****	*.190***	*.191***
4.Distress (HADS-t)				.922***	.891***	.773***	*.469****	*.789****	.498***	.477***	*.671****
5.Anxiety (HADS-A)					.646***	.751***	*.512****	*.813****	.409***	.530***	*.679****
6.Depression (HADS-D)						.643***	*.312****	*.583****	.502***	.320***	*.520****
7. Cognitive Attentional Syndrome (CAS-10)							*.464****	*.732****	.442***	.542***	*.638****
8. Positive Metacognitive Beliefs (MCQ-30)								*.446****	*.222****	*.455****	*.532****
9. Negative Metacognitive Beliefs (MCQ-30)									*.402****	*.587****	*.751****
10. Lack of Cognitive Confidence (MCQ-30)										.270**	*.332****
11. Cognitive Self-consciousness (MCQ-30)											.594***
12. Need to Control Thoughts (MCQ-30)											

Note: CAS-10 = Cognitive Attentional Syndrome Questionnaire (Wells, 2008); CFQ-11 = Chalder Fatigue Scale, 11 item version, (Cella & Chalder, 2010; Chalder et al., 1993); HADS-t = Total Distress (Hospital and Anxiety Scale, Zigmond & Snaith, 1983); HADS-A = Anxiety; HADS-D = Depression; MCQ-30 = Metacognitions Questionnaire-30 (Wells & Cartwright-Hatton, 2004)

* $p < 0.05$; ** $p < 0.01$, *** $p < 0.01$

Spearman's correlations are italicized.

Metacognitive Beliefs, Depression and Anxiety

Table 3 displays the hierarchical regression models examining the relationship between metacognitive beliefs and both anxiety and depression, whilst controlling for demographic and clinical variables. Inspection of histograms indicated normal distribution of standardized residuals. Plots indicated no evidence of heteroscedascity. Cook's distances did not exceed one, indicating no undue influence exerted upon the regression models by a single case. There was no evidence of multicollinearity (variance inflation factors < 5, tolerance statistics > 0.2). Variance inflation factors ranged between 1.032 and 3.326 and tolerance statistics ranged between .301 and .969.

In the depression model, age (step 1) was non-significant (*F*change = .942, *df* =1,233 *p* = .333). Entered at step 2, time since CFS/ME onset and comorbidity with at least one listed condition (Fibromyalgia/Chronic Pain/IBS) were statistically significant (*F*change = 6.556, *df* = 2,231, *p* = .002), accounting for an additional 5.3% of the variance. Level of fatigue (step 3) and the CAS (step 4) were also statistically significant, (*F*change = 25.132, *df* = 1,230, *p* < .001; *F*change = 135.966, *df = 1,229, p* < .001), accounting for an additional 9.3% and 31.7% of the variance in depression respectively. Consistent with hypothesis 3, metacognitive beliefs entered in the final step made a significant contribution (*F*change = 8.152, *df*= 5,224, *p* < .001), accounting for an additional 8.2% of the variance. Overall, the model accounted for 54.9% of the variance in depression (R^2 = .549, *F* (10, 224) = 27.263, *p* < .001). There were six independent predictors of depression in the final model; age (β = .206 *p* < 0.001); fatigue (β = .116 *p* = .025; the CAS (β = .372, *p* < .001); NMCB (β = .245, *p* = .003); LCC (β = .190, *p* < .001) and CSC (β = -.148. *p* < .013).

In the model examining anxiety, demographic and clinical variables entered at each step were statistically significant. Age (step 1) accounted for 2.9% of the variance (*F*change = 6.995, *df* =1,233, *p* = .009). Time since CFS/ME onset and comorbidity with at least one

listed condition (step 2) accounted for an additional 11.7% of the variance (*F*change = 15.771, *df* =2,231, $p < .001$). Fatigue (step 3) accounted for an additional 5.% of the variance (*F*change = 14.448 , *df* =1,230 $p < .001$). The CAS (step 4) accounted for an additional 38.7% of the variance (*F*change = 212.347, *df* = 1,229, $p < .001$). Consistent with hypothesis 3, metacognitive beliefs (step 5) made a significant contribution, accounting for an additional 14.5% of the variance in anxiety (*F*change = 23.760, *df* = 5,224, $p < .001$). Overall, the model predicted 72.7 % of the variance in anxiety ($R^2 = .727$, *F* (10,224) = 59.801, $p < .001$). In the final model, there were three independent predictors of anxiety; the CAS ($\beta = .268$, $p < .001$); PMCB ($\beta = .169$ $p < .001$); and NMCB ($\beta = .520$, $p < .001$); fatigue was not associated with anxiety ($\beta = .075$, $p = .063$).

Table 3

Hierarchical Regression Models Predicting Depression and Anxiety.

		Depression								***Anxiety***							
									95% confidence intervals								***95% confidence intervals***
	Predictor	***R^2***	***Adj R^2***	***ΔR^2***	***b***	***SE***	***β***	***p***	***LL***	***UL***	***R^2***	***Adj R^2***	***ΔR^2***	***b***	***SE***	***β***	***p***	***LL***	***UL***
Step1																			
	Age				*.024*	*.024*	*.063*	*.333*	*-.024*	*.072*				*-.075***	*.028*	*-.171***	*.009*	*-.131*	*-.019*
		.004	*.000*	*.004*				*.333*			*.029*	*.025*	*.029*				*.009*		
Step 2																			
	Age				*.059*	*.027*	*.159*	*.026*	*.007*	*.112*				*-.025*	*.030*	*-.057*	*.402*	*-.084*	*.034*
	Onset				*-.077*	*.035*	*-.154*	*.029*	*-.145*	*-.008*				*-.084*	*.039*	*-.144*	*.031*	*-.161*	*-.008*
	Other illness				*1.924*	*.643*	*.194*	*.003*	*.656*	*3.191*				*3.802*	*.719*	*.327*	*<.001*	*2.386*	*5.218*
		.058	*.045*	*.053*				*.003*			*.146*	*.135*	*.117*				*<.001*		
Step 3																			
	Age				*.058*	*.025*	*.154*	*.023*	*.008*	*.108*				*-.026*	*.029*	*-.060*	*.362*	*-.083*	*.031*
	Onset				*-.033*	*.034*	*-.066*	*.340*	*-.100*	*.035*				*-.046*	*.039*	*-.079*	*.237*	*-.124*	*.031*
	Other illness				*1.474*	*.619*	*.149*	*.018*	*.255*	*2.692*				*3.412*	*.706*	*.293*	*<.001*	*2.021*	*4.803*
	Fatigue				*.262*	*.052*	*.320*	*<.001*	*.159*	*.364*				*.226*	*.060*	*.236*	*<.001*	*.109*	*.344*
		.150	*.136*	*.093*				*<.001*			*.196*	*.182*	*.050*				*<.001*		
Step 4					*.071*	*.020*	*.189*	*<.001*	*.031*	*.110*				*-.010*	*.021*	*-.022*	*.648*	*-.051*	*.032*
	Age				*.005*	*.027*	*.009*	*.867*	*-.049*	*.059*				*.002*	*.028*	*.004*	*.941*	*-.054*	*.058*
	Onset				*-.049*	*.508*	*-.005*	*.924*	*-1.050*	*.952*				*1.438*	*.527*	*.124*	*.007*	*.398*	*2.477*
	Other illness				*.128*	*.043*	*.157*	*.003*	*.043*	*.213*				*.053*	*.045*	*.056*	*.234*	*-.035*	*.141*
	Fatigue				*.021*	*.002*	*.627*	*<.001*	*.018*	*.025*				*.028*	*.002*	*.693*	*<.001*	*.024*	*.031*
	CAS				*.071*	*.020*	*.189*	*<.001*	*.031*	*.110*	*.583*	*.574*	*.387*				*<.001*		
								<.001						*-.010*	*.021*	*-.022*	*.648*	*-.051*	*.032*

Table 3

continued

	Depression									Anxiety								
								95% confidence intervals									95% confidence intervals	
Predictor	**R^2**	**Adj R^2**	**ΔR^2**	**b**	**SE**	**β**	**p**	**LL**	**UL**	**R^2**	**Adj R^2**	**ΔR^2**	**b**	**SE**	**β**	**p**	**LL**	**UL**
Step 5																		
Age				*.077*	*.019*	*.206*	*<.001*	*.039*	*.115*				*.024*	*.018*	*.054*	*.179*	*-.011*	*.058*
Onset				*-.009*	*.026*	*-.017*	*.740*	*-.059*	*.042*				*-.005*	*.023*	*-.009*	*.828*	*-.051*	*.041*
Other llness				*-.552*	*.481*	*-.056*	*.253*	*-1.50*	*.396*				*.623*	*.439*	*.054*	*.157*	*-.242*	*1.488*
Fatigue				*.095*	*.042*	*.116*	*.025*	*.012*	*.178*				*.072*	*.038*	*.075*	*.063*	*-.004*	*.147*
CAS				*.013*	*.002*	*.372*	*<.001*	*.008*	*.017*				*.011*	*.002*	*.268*	*<.001*	*.006*	*.015*
PMCB				*.098*	*.069*	*.081*	*.158*	*-.038*	*.234*				*.238*	*.063*	*.169*	*<.001*	*.114*	*.362*
NMCB				*.211*	*.070*	*.245*	*.003*	*.072*	*.350*				*.525*	*.064*	*.520*	*<.001*	*.399*	*.652*
LCC				*.169*	*.048*	*.190*	*<.001*	*.075*	*.264*				*.013*	*.044*	*.013*	*.763*	*-.073*	*.099*
CSC				*-.163*	*.065*	*-.148*	*.013*	*-.292*	*-.034*				*-.011*	*.060*	*-.009*	*.853*	*-.129*	*.107*
NCT				*.108*	*.084*	*.097*	*.199*	*-.058*	*.274*				*-.017*	*.077*	*-.013*	*.821*	*-.169*	*.134*
	.549	*.529*	*.082*				*<.001*			*.727*	*.715*	*.145*				*<.001*		

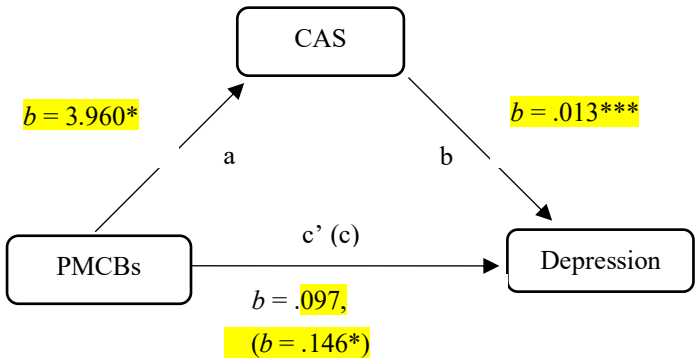
Note: Adj R^2 = adjusted R^2 ; CAS = cognitive attentional syndrome; CSC = cognitive self-consciousness LCC = lack of cognitive confidence; LL = lower limit; NCT = need to control thoughts; NMCB = negative metacognitive beliefs; Onset = time since CFS/ME onset; PMCB = positive metacognitive beliefs; SE = standard error; UL = upper limit.

Mediation Analyses

The model which assessed the role of the CAS in mediating the relationship between PMCBs and depression (fig 2) indicated full mediation; the direct effect between PMCBs and depression was no longer significant, when accounting for the CAS (b = .097, t (226) = 1.404, p = .162).

Fig. 1.

Mediation of Association Between PMCBs and Depression via the CAS.



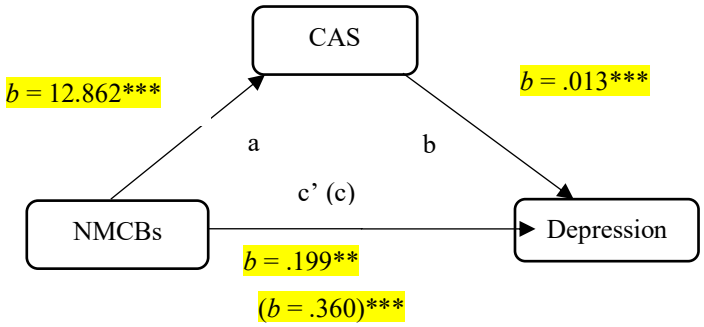
Indirect effect = .050, BCa 95% CIs = .006 to .104

Note: BCa = bias-corrected and accelerated bootstrap; CAS = cognitive attentional syndrome; PMCBs = positive metacognitive beliefs.
Model covariates: age; fatigue; negative metacognitive beliefs; cognitive self-consciousness; lack of cognitive confidence; beliefs about the need to control thoughts.
Bootstrapping with 5000 samples.
* = p < .05; *** = p <.001

The model which assessed the role of the CAS in mediating the relationship between NMCBs and depression (fig 2) indicated partial mediation; the direct effect between NMCBs and depression remained significant, when accounting for the CAS (b = .199, t (226) = 2.850, p = .005).

Fig. 2.

Mediation of Association Between NMCBs and Depression via the CAS.



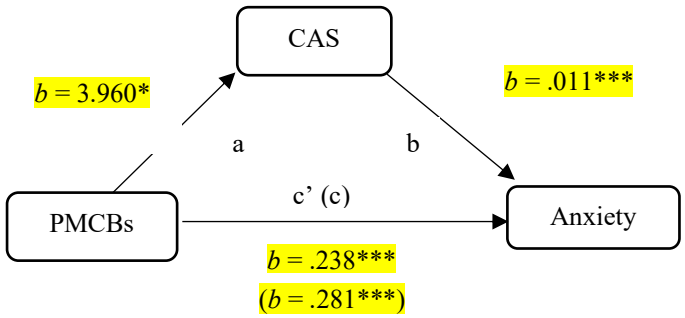
Indirect effect = .161, BCa 95% CIs = .085 - .253

Note: BCa = bias-corrected and accelerated bootstrap; CAS = cognitive attentional syndrome; NMCBs = negative metacognitive beliefs.
Model covariates: age; fatigue; positive metacognitive beliefs; cognitive self-consciousness; lack of cognitive confidence; beliefs about the need to control thoughts.
Bootstrapping with 5000 samples.
** = p <.01; *** = p < .001.

The model which assessed the role of the CAS in mediating the relationship between PMCBs and anxiety (fig.3) indicated partial mediation; the direct effect between PMCBs and anxiety remained significant, when accounting for the CAS (b = .238, t (226) = 3.781 , p < .001). The model which assessed the role of the CAS in mediating the relationship between NMCBs and anxiety (fig. 4) indicated partial mediation; the direct effect between NMCBs and anxiety remained significant, when accounting for the CAS (b = .537 p < .001).

Fig. 3.

Mediation of Association Between PMCBs and Anxiety via the CAS.

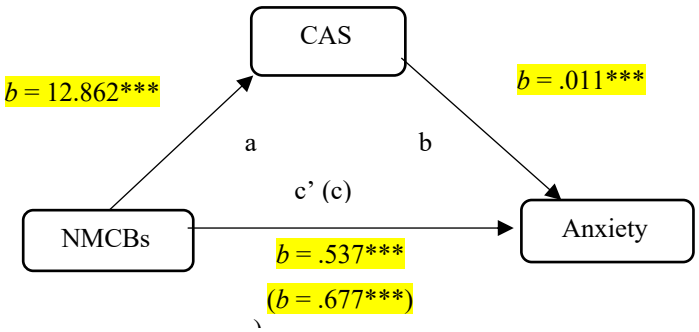


Indirect effect = .043, BCa 95% CIs = .003- .095

Note: BCa = bias-corrected and accelerated bootstrap; CAS = cognitive attentional syndrome; PMCBs = positive metacognitive beliefs.
Model covariates: age; fatigue; negative metacognitive beliefs; cognitive self-consciousness; lack of cognitive confidence; beliefs about the need to control thoughts.
Bootstrapping with 5000 samples.
* = p < .05; *** = p < .001;

Fig. 4.

Mediation of Association Between NMCBs and Anxiety via the CAS.



Indirect effect = .139, BCa 95% CIs = .068 - .223

Note: BCa = bias-corrected and accelerated bootstrap; CAS = cognitive attentional syndrome; NMCBs = negative metacognitive beliefs.
Model covariates: age; fatigue; positive metacognitive beliefs; cognitive self-consciousness; lack of cognitive confidence; beliefs about the need to control thoughts.
Bootstrapping with 5000 samples.
*** = p < .001.

Discussion

Consistent with existing evidence (Fischler et al., 1997; Fuller-Thomson & Nimigon, 2008; Iwase et al., 2008; White et al., 2011), higher levels of depression and anxiety were reported in this sample, compared to the general population (McManus, et al., 2016). Both metacognitive beliefs and the CAS were significantly and positively associated with both depression and anxiety; analyses indicated moderate-strong associations. When controlling for demographic and clinical variables including fatigue, metacognitive beliefs accounted for an additional 8.2% and 14.5% of the variance in depression and anxiety respectively. Consistent with hypothesis 4, the CAS fully mediated the relationship between positive metacognitive beliefs and depression; partial mediation by the CAS was indicated for the relationships between positive metacognitive beliefs and anxiety, and between negative metacognitive beliefs and both depression and anxiety. These findings are consistent with previous research examining the utility of the S-REF model in physical health populations (Cook et al., 2015; Heffer-Rahn & Fisher, 2018) and the underlying theory.

Implications for theory

The S-REF model proposes that beliefs about the usefulness of worry and rumination lead both directly and indirectly to anxiety and depression. Operating at a low level of conscious awareness, these PMCBs activate perseverative thought processes, threat-focussed attention, and maladaptive cognitive and behavioural coping strategies. Together these processes form the CAS. In the case of anxiety, perseverative thinking is characterized by worry and in the case of depression, by rumination. According to the S-REF model, these strategies backfire, as NMCBs cause worry/rumination to be perceived as uncontrollable and dangerous.

Differential outcomes for anxiety and depression in this study are broadly consistent with the S-REF model. Both positive and negative metacognitive beliefs are implicated in the metacognitive model of Generalized Anxiety Disorder (GAD, Wells, 2009); in response to a trigger, PMCBS activate the selection of worry as a strategy, which in turn activates NMCBs about the uncontrollability and danger of worry and subsequently, the CAS. This is reflected in the final regression model, where the three independent statistical predictors of anxiety were both positive and negative metacognitive beliefs and the CAS.

The metacognitive model of depression proposes PMCBs activate depressive rumination as a strategy to overcome problems, including depression itself. This in turn activates NMCBs about the uncontrollability of rumination. Although PMCBs did not make as an independent contribution to depression in the final regression model ($\beta = .081$, $p = .158$), the CAS fully mediated the association between PMCBs and depression; findings suggest it is not the PMCB which underpin selection of rumination as a strategy which is significant, but rather depressive rumination itself, which is a central feature of the CAS (Wells, 2009). Findings from the regression analysis corroborate the centrality of NMCBs and the CAS, as outlined in the metacognitive model of depression.

The S-REF model (Wells & Matthews 1994) proposes that higher levels of cognitive self-consciousness (CSC) will be associated with more severe depression. However, in the present study, higher CSC was associated with lower levels of depression. A comparable find was obtained when examining metacognitive beliefs and depression in people living with multiple sclerosis (Heffer-Rahn & Fisher, 2018). The negative association between cognitive self-consciousness and depression may reflect an avoidance strategy which limits distress in the short term but is counterproductive in the longer term. More specifically, people are monitoring their minds for the presence of negative thoughts but are using a range of suppression strategies to remove those thoughts as rapidly as possible. If suppression

strategies no longer remove the thoughts then it is possible that this will activate NMCBs thereby increasing distress (Palmier-Claus et al., 2013; Wells, 1997). The positive association between LCC and depression is consistent with predictions of the S-REF model (Wells & Matthews 1994); LCC may be a consequence of depressive rumination, which further perpetuates depression (Papageorgiou & Wells, 2003). Specifically, perseverative negative thinking may detract from other aspects of cognition, thereby reducing confidence in one's own memory, concentration and attention.

Study Limitations

This study offers preliminary evidence that both metacognitive beliefs and the CAS contribute to co-morbid depression and anxiety in CFS/ME. However, conclusions must be drawn with caution, given the cross-sectional nature of the research. This is arguably a particular concern in mediation analysis (Wiederman & von Eye., 2015), whereby the causality could be reversed or indeed bi-directional. As well as contributing to depression and anxiety, the strength of metacognitive beliefs could fluctuate in *response* to varying levels of depression and / or anxiety. Such dynamic relationships may be mediated by the CAS. Nevertheless, predictions were based upon empirical evidence. This initial study provides a basis for further longitudinal research to corroborate directions of causality.

Despite recruitment from three specialist clinics, this represented only 6.8% of respondents. This is hypothesized to reflect at least in part, comparative ease of accessibility via the advertisement online. Nevertheless, the study sought to recruit a large, representative sample including both those open to specialist CFS/ME services, and those who were not. Two million adults living with CFS/ME in the UK are unable to access specialist services (Collin, Sterne, Hollingworth, May, & Crawley, 2012). Furthermore, due to the nature and duration of the illness, patients are likely to be discharged following non-curative, time-

limited interventions, whilst still experiencing symptoms to some degree. Recruitment from online support groups offers this population opportunity to engage with research.

Whilst self-confirmation of a clinical diagnosis was a requirement for participation, confirmation from a health professional would have increased methodological rigour. Nevertheless, such increased stringency was beyond the scope of this study and may have impacted upon the representativeness of the sample. Furthermore, the likelihood of a reduced sample size would have had implications for statistical power. Most participants (93.6%) exceeded the CFQ-11 cut off scores for clinical caseness; scores not meeting this threshold may be attributable to fluctuations in symptom severity across the course of the illness and possible progress towards recovery.

In order to minimise participant burden, measures of secondary symptoms were not included. It was therefore not possible to statistically control for cognitive symptoms such as difficulties with short-term memory, attention and concentration (Carruthers et al., 2011), which may overlap or interact with LCC. There is likely to be a dynamic relationship between the cognitive symptoms themselves and reduced personal confidence in these abilities (LCC). This may be mediated by factors such as anxiety. For example, experiencing difficulties in concentration may lead to anxiety about one's ability to concentrate, which may reduce confidence in this ability. Furthermore, this may drive worry and rumination, potentially further reducing the cognitive capacity for concentration. Future studies may therefore consider broader symptom measures or subscales (Jason et al., 2015; Sunnquist et al., 2019) to facilitate more complex statistical analysis.

Despite the selection of shortened versions of psychometric measures in this study, those most severely affected are less likely to take part in research due to the impact of their symptoms (Strassheim et al., 2018). Similarly, correspondence was received by the authors indicating a proportion of the CFS/ME population reject the relevance of psychological

research; this suggests a further sub-group who are likely to be un-represented. These are nevertheless broader issues in CFS/ME research, rather than this study per se.

Clinical implications

The S-REF model provides a theoretical basis for understanding comorbid depression and anxiety in CFS/ME. When controlling for relevant demographic and clinical variables including level of fatigue, metacognitive beliefs accounted for additional variance in depression and anxiety. The relationship between positive and negative metacognitive beliefs operated indirectly through the CAS. Translated into clinical practice, this indicates the potential therapeutic benefits of counteracting perseverative thinking, attentional focus, and unproductive coping strategies, as well as the metacognitive beliefs which underpin their selection and continuation. Metacognitive therapy (Wells, 2009) may be effective in modifying metacognitive beliefs and the CAS

Longitudinal research is required to examine whether metacognitive beliefs are vulnerability markers for persistent anxiety and depression in CFS/ME. Early identification of metacognitive beliefs, perseverative thought processes and coping strategies could reduce the emotional distress experience by people with CFS/ME.

Conclusion

MCT may be effective in reducing co-morbid depression and anxiety in people living with CFS/ME. In targeting metacognitive processes which maintain distress, as opposed to questioning the validity of illness-related cognitions, MCT may be acceptable to this patient group. Within the context of controversy surrounding the role of psychological approaches, MCT has the potential to offer an efficacious psychological intervention, as part of a living well with chronic illness approach.

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Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361-370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Appendix A: Extracts from Author Guidelines for the Journal of Psychosomatic Research

Review Articles

Review papers are normally systematic reviews following the PRISMA statement of 4000-5000 words (Introduction through Discussion).

NEW SUBMISSIONS

Formatting requirements

There are no strict formatting requirements but all manuscripts must contain the essential elements needed to convey your manuscript, for example Abstract, Keywords, Introduction, Materials and Methods, Results, Conclusions, Artwork and Tables with Captions.

If your article includes any Videos and/or other Supplementary material, this should be included in your initial submission for peer review purposes.

Divide the article into clearly defined sections.

Figures and tables embedded in text

Figures and the tables included in the single file can be placed next to the relevant text in the manuscript or at the bottom of the file. The corresponding caption should be placed directly below the figure or table.

References

There are no strict requirements on reference formatting with new submissions. References can be in any style or format as long as the style is consistent. Where applicable, author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume number/book chapter and the article number or pagination must be present. Use of DOI is

highly encouraged. Revisions should be submitted in the *Journal of Psychosomatic Research* format as the reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that missing data will be highlighted at proof stage for the author to correct.

Submissions

Manuscripts should conform to the uniform requirements known as the 'Vancouver style' (International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309-315).

Reference style

Text: Indicate references by number(s) in square brackets in line with the text. The actual authors can be referred to, but the reference number(s) must always be given.
List: Number the references (numbers in square brackets) in the list in the order in which they appear in the text.

Revised submissions

Title Page This should contain (a) the title of the article; (b) a short running head; (c) name of department where the work was conducted; (d) names of each author with highest academic degree; (e) name, address, phone and fax of author responsible for correspondence and to whom requests for reprints should be addressed. Structured Abstract This should be subdivided under the headings Objective, Methods, Results, and Conclusion and should not exceed 250 words. Be sure that key information, such as study design and sample size are included. For primary results, include some measure of the magnitude of the association and not simply a p-value. Keywords Up to six keywords should be listed in alphabetical order after the abstract. These terms should optimally characterize the paper to facilitate choice of

peer reviewers. Article Structure The text should be divided into sections with main headings: Introduction, Method, Results and Discussion and, in total, these sections should not normally be greater than 4000 words in length. Acknowledgements Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. Acknowledgements must include mention of any source of funding outside the basic funding of the host institution (see Role of the funding source above). List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.). Tables Number tables consecutively in accordance with their appearance in the text. Place footnotes to tables below the table body and indicate them with superscript lowercase letters. Any abbreviations used should be included in the footnotes with enough information for the reader to understand without referring back to the text. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article. Figures Each should be on a separate sheet, and numbered consecutively. Captions should be on a separate sheet. Any abbreviations used should be included in the captions with enough of a description for the figures to be interpreted independently from the text. The number of illustrations should be kept to a minimum. Colour illustrations are not normally acceptable. Authors may be asked to support the costs of colour reproduction.

Abbreviations

Keep abbreviations to a minimum and avoid their use in the abstract. Spell out each abbreviation in the text the first time that it is used. Ensure consistency of abbreviations throughout the article.

Footnotes

Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors build footnotes into the text, and this feature may be used. Should this not be the case, indicate the position of footnotes in the text and present the footnotes themselves separately at the end of the article.

References

These should be numbered consecutively in the text in the order in which they are first mentioned and be so denoted in the list. Their form should be that adopted by the US National Library of Medicine, as used in the Index Medicus and as recommended in Huth EJ, Medical Style and Format. Reference links Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is highly encouraged.

Appendix B: Extract from British Journal of Health Psychology

MANUSCRIPT CATEGORIES AND REQUIREMENTS

Papers describing quantitative research (including reviews with quantitative analyses) should be no more than 5000 words (excluding the abstract, reference list, tables and figures).

PREPARING THE SUBMISSION

Free Format Submission

British Journal of Health Psychology now offers free format submission for a simplified and streamlined submission process.

Before you submit, you will need:

- Your manuscript: this can be a single file including text, figures, and tables, or separate files – whichever you prefer. All required sections should be contained in your manuscript, including abstract, introduction, methods, results, and conclusions. Figures and tables should have legends. References may be submitted in any style or format, as long as it is consistent throughout the manuscript. If the manuscript, figures or tables are difficult for you to read, they will also be difficult for the editors and reviewers. If your manuscript is difficult to read, the editorial office may send it back to you for revision.
- The title page of the manuscript, including a data availability statement and your co-author details with affiliations.

The title page should contain**:**

- A short informative title containing the major key words. The title should not contain abbreviations

- A short running title of less than 40 characters
- The full names of the authors
- The author's institutional affiliations where the work was conducted, with a footnote for the author's present address if different from where the work was conducted
- Abstract
- Keywords
- Data availability statement (see Data Sharing and Data Accessibility Policy);
- Acknowledgments.

Abstract

For articles containing original scientific research, a structured abstract of up to 250 words should be included with the headings: Objectives, Design, Methods, Results, Conclusions.

Revised submissions

References

References should be prepared according to the *Publication Manual of the American Psychological Association* (6th edition). This means in text citations should follow the author-date method whereby the author's last name and the year of publication for the source should appear in the text, for example, (Jones, 1998). The complete reference list should appear alphabetically by name at the end of the paper. Please note that for journal articles, issue numbers are not included unless each issue in the volume begins with page 1, and a DOI should be provided for all references where available.

Tables

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be

concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Appendix C: Quality Assessment Tool – Adapted from Williams et al., (2010)

General instructions: Grade each criterion as "Yes," "No," "Partially," or "Can't tell." Factors to consider when making an assessment are listed under each criterion. Criteria marked *italics* are considered the most essential quality indicators for our purposes.

1. ***Unbiased selection of the cohort?***

   Factors that help *reduce* selection bias:

   - Inclusion/exclusion criteria
     - Clearly described diagnostic criteria for CFS/ME and/ or additional assessments e.g. psychiatric assessment, assessment by a physician, biological tests to rule out other causes of physical symptoms
     - Assessed using valid and reliable measures of fatigue / physical symptoms.
   - Recruitment strategy
     - Clearly described
     - Relatively free from bias (selection bias might be introduced, e.g., by recruitment via advertisement; at a particular stage in diagnosis / treatment; consecutively admitted patients)

2. **Sample size calculated/5% difference?**

   Factors to consider:

   - Did the authors report conducting a power analysis or describe some other basis for determining the adequacy of study group sizes for the primary outcome(s) of interest to us?
   - Was the sample size sufficiently large to detect a clinically significant difference of 5% in event rates or an OR/RR increase of ≥ 1.5 or decrease of ≥ 0.67 between groups in at least one primary outcome measure of interest to us?

3. **Adequate description of the cohort?**

   Consider whether the cohort is well-characterized in terms of baseline:

   - Age
   - Sex
   - Race
   - Educational level
   - Time since CFS/ME symptom onset
   - Mean level of fatigue
   - Mean level of anxiety and depression / clinical caseness

- Level of cognitive symptoms

4. ***Validated measures of depression / anxiety / perfectionism?***

   Factors to consider:

   - Were the psychometric measures clearly described and referenced?
   - Were validated psychometric measures used?

5. ***Analysis controls for confounding?***

   Factors to consider:

   - Does the study identify and control for important confounding variables e.g. level of cognitive symptoms, time since CFS/ME onset.

6. ***Analytic methods appropriate?***

   Factors to consider:

   - Was the kind of analysis done appropriate for the kind of outcome data?
   - Was the number of variables used in the analysis appropriate for the sample size? (The statistical techniques used must be appropriate to the data and take into account issues such as controlling for small sample size, clustering, rare outcomes, multiple comparison, and number of covariates for a given sample size.

Appendix D: Approval Letter from the University of Liverpool Research Review Committee

UNIVERSITY OF LIVERPOOL

D.Clin.Psychology Programme
Division of Clinical Psychology
Whelan Building, Quadrangle
Brownlow Hill
LIVERPOOL
L69 3GB

Tel: 0151 794 5530/5534/5877
Fax: 0151 794 5537
www.liv.ac.uk/dclinpsychol

Amelia Wright
Clinical Psychology Trainee
Doctorate of Clinical Psychology Doctorate Programme
University of Liverpool
L69 3GB

17 October 2018

RE: Are metacognitive processes associated with distress in people with chronic fatigue symptoms? Trainee: Amelia Wright
Supervisors: Peter Fisher & Gemma Cherry

Dear Amelia,

Thank you for your response to the reviewers' comments of your research proposal submitted to the D.Clin.Psychol. Research Review Committee.

I can now confirm that your amended proposal (version number 3, dated October 2018) meets the requirements of the committee and has been approved by the Committee Chair.

Please take this Chairs Action decision as ***final*** approval from the committee.

You may now progress to the next stages of your research.

I wish you well with your research project.

Dr Catrin Eames
Vice-Chair D.Clin.Psychol. Research Review Committee.

Appendix E: University of Liverpool Sponsorship Approval Letter

Miss Lara Lavelle-Langham
Research Integrity and Governance Manager

University of Liverpool
Research Support Office
2nd Floor Block D Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

Tel: 0151 794 8373
Email: sponsor@liverpool.ac.uk

27/08/2019

RE: 4246 - Are metacognitive processes associated with distress in people with Chronic Fatigue Symptoms?

Dear Dr Fisher,

All necessary documentation and regulatory approvals have now been received by the University of Liverpool Research Support Office in its capacity as Sponsor, and we are satisfied that all Clinical Research Governance requirements have been met. You may now proceed with any study specific procedures to open the study.

The following HRAApproved documents have been received by the Research Support Office. Only these documents can be used in the recruitment of participants. If any amendments are required please contact the Research Support Office:

Document Type	File Name	Date	Version
Other Essential Documentation	Approved 1 page research summary		
Evidence Of Peer Review	Wright Amelia_Approval	18/10/2018	1
Other Participant Documentation	MCQ-30	05/12/2018	1
Other Participant Documentation	HADS	05/12/2018	1
Other Participant Documentation	Poster Advert for services CFS V2	04/01/2019	2
Other Participant Documentation	demographics	04/01/2019	1
Other Participant Documentation	Online Advert CFS V2	04/01/2019	2
Other Participant Documentation	Study Debrief Form CFS version 3	04/01/2019	3
Other Participant Documentation	CAS CFS version 1	04/01/2019	1
Other Participant Documentation	Chalder fatigue scale	04/01/2019	1
Participant Consent Form	Participant Consent Form CFS version 4	24/01/2019	4
Project Protocol/Clinical Investigation Plan	Approved Research Proposal - sponsorship Jan 19	12/07/2019	5

Please note, under the terms of your Sponsorship you must:

- Gain NHS Confirmation of Capacity and Capability from each participating site before recruitment begins at that site;
- Ensure all required contracts are fully executed before recruitment begins at any site;
- Inform the Research Support Office as soon as possible of any adverse events especially SUSARs and SAE's, Serious Breaches to protocol or relevant legislation or any concerns regarding research conduct;
- Approval must be gained from the Research Support Office for any amendments to, or changes of status in the study prior to

submission to REC and any other regulatory authorities (as per SOP018);

- It is a requirement that Annual Progress Reports are sent to the NHS Research Ethics Committee (REC) annually following the date of Favourable Ethical Approval. You must provide copies of any reports submitted to REC and other regulatory authorities to the Research Support Office;
- Maintain the study master file (as per SOP005);
- Make available for review any study documentation when requested by the sponsors and regulatory authorities for the purposes of audit or inspection;
- Upon the completion of the study it is a requirement to submit an End of Study Declaration (within 90 days of the end of the study) and End of Study Report to REC (within 12 months of the end of the study). You must provide copies of this to the Research Support Office;
- Ensure you and your study team are up to date with the current RSO SOPs throughout the duration of the study.

If you have any queries regarding the sponsorship of the study, please do not hesitate to contact the Clinical Research Governance Team on 0151 794 8373 (email sponsor@liverpool.ac.uk).

Yours sincerely,

Miss Lara Lavelle-Langham
Research Integrity and Governance
Manager Research Support Office

Appendix F: Heath Research Authority Approval Letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Peter Fisher
University of Liverpool
Wheelan Building, The Quadrangle
Brownlow Hill, Liverpool
L69 3GB

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

30 May 2019

Dear Dr Fisher

Initial Assessment Letter

Study title:	**Are metacognitive processes associated with distress in people with chronic fatigue symptoms?**
IRAS project ID:	**253333**
Protocol number:	**UoL001442 - 4246**
REC reference:	**19/NW/0406**
Sponsor	**University of Liverpool**

Thank you for your application for HRA and Health and Care Research Wales (HCRW) Approval. I am writing to confirm that you are now able to share the Local Information Pack with participating NHS organisations in England and Wales in order to invite them to arrange of capacity and capability to deliver your study. Please note that **the research should not begin** at any participating NHS organisations in England or Wales until HRA and HCRW Approval is issued.

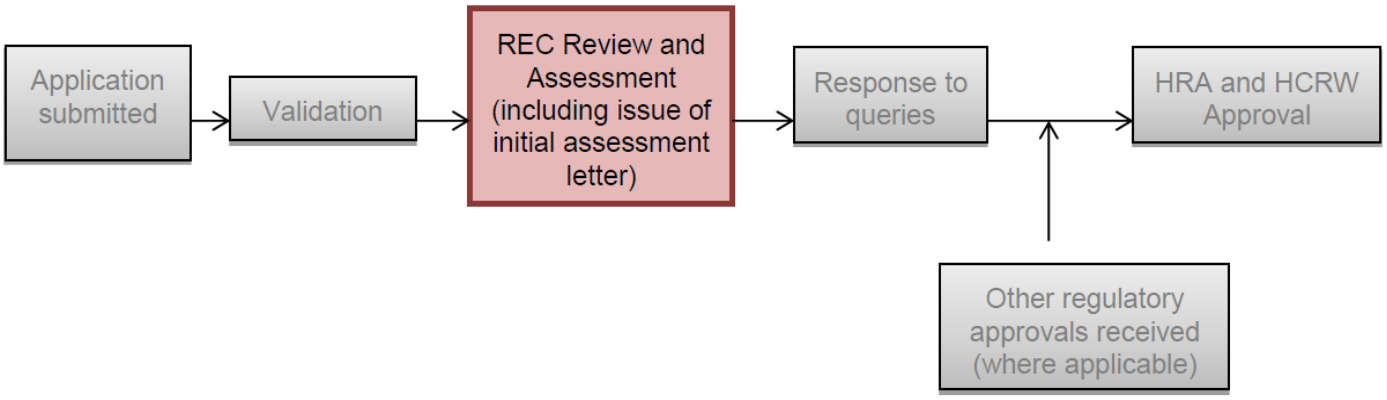
To share the Local Information Pack with participating NHS organisations in England and Wales please use the template email available on the IRAS website.

Once the Local Information Pack has been shared, please work with participating NHS organisations to arrange capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

What happens next with my application for HRA and HCRW Approval?

IRAS project ID	**253333**

Your application is progressing. Please find below an indication of where you are in the process (indicated by the red box).



I am undertaking the assessment of the application and you will receive any queries following the REC meeting.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations in Northern Ireland and Scotland.

If you indicated in your IRAS form that you have participating organisations in Northern Ireland and/or Scotland, the national coordinating function of each participating nation has been informed and provided with the initial document set. The relevant national coordinating function/s will contact you as appropriate. We will provide them the final document set and study wide governance report when available.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?

HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

Who should I contact for further information?

Please do not hesitate to contact me for assistance with this application. My contact details are below.

IRAS project ID	**253333**

Your IRAS project ID is 253333. Please quote this on all correspondence

Yours sincerely,

Isobel Lyle
HRA Approvals Manager
Health Research Authority
NHSBT Newcastle Blood Donor Centre | Holland Drive | HRA Newcastle | NE2 4NQ
T. 0207 972 2496
E. isobel.lyle@nhs.net
W. www.hra.nhs.uk

Copy to: *Mr Alex Astor*

Information to support study set up

The below provides all parties with information to support the arranging of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter. As part of the application process, details may change prior to a Letter of HRA and HCRW Approval being issued.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is one site type where all site activities will be undertaken.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	A statement of activities has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	No application for funding is being made. Details of resource materials being made available to sites are included in the Statement of Activities	A Local Collaborator is required at each site and named LC's are in place	It is unlikely that letters of access or honorary research contracts will be applicable, however, for research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate, if required.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio

Appendix G: Poster Advertisement

UNIVERSITY OF LIVERPOOL

Emotional Distress and Chronic Fatigue Symptoms

Have you been diagnosed with Chronic Fatigue Syndrome (CFS) / Myalgic Encephalomyelitis (ME)?

We are looking for people between the ages of 18 and 75 to help us understand the emotional distress which may be experienced with chronic fatigue symptoms.

If you would like to take part, please type this link into your browser to complete the online survey:

https://livpsych.eu.qualtrics.com/jfe/form/SV_7Qmtc2kcNN7d0aN

(This will take approximately 20-30 minutes to complete)

Alternatively, please ask you clinician for a paper copy.

To thank you for time and effort in taking part, you can choose to be entered into a prize draw for one of ten £15 Amazon Vouchers.

Researcher: Amelia Wright, Liverpool University: amelia.wright@liverpool.ac.uk

Appendix H: Consent to Contact Form

Consent to Contact Form

We are currently completing research into ME / CFS in conjunction with the University of Liverpool
If you are between 18 and 75 and you may be interested in participating, please complete this form and return it to your clinician / clinic administration staff to receive further information.

Please select one of the following:

I would prefer to receive:

☐ A paper advertisement with a web link to further information and an online survey.

☐ A participant information sheet and a paper survey.

I consent to receiving further written information regarding this research.

Signed: ……. date:…….

Print: …….

UNIVERSITY OF LIVERPOOL

Emotional Distress and Chronic Fatigue Symptoms

Have you been diagnosed with Chronic Fatigue Syndrome (CFS) / Myalgic Encephalomyelitis (ME)?

We are looking for people between the ages of 18 and 75 to help us understand the emotional distress which may be experienced with chronic fatigue symptoms.

If you would like to take part, please type this link into your browser to complete the anonymous online survey:

https://livpsych.eu.qualtrics.com/jfe/form/SV_7Qmtc2kcNN7d0aN

(This will take approximately 20-30 minutes to complete)

Alternatively, to receive a paper copy, please contact the Researcher, Amelia Wright:
amelia.wright@liverpool.ac.uk
University of Liverpool, Whelan Building, Brownlow Hill, Liverpool, L69 3GB.

To thank you for time and effort in taking part, you can choose to be entered into a prize draw for one of ten £15 Amazon Vouchers.

Online advert Version 5. 01/09/19

Appendix J: Participant Information Sheet

PARTICIPANT INFORMATION SHEET

Emotional Distress and Chronic Fatigue Symptoms

Project Research Ethics Number: 253 333

We are inviting you to participate in a research study. Before you decide whether to participate, it is important for you to understand why the research is being done and what it involves. Please take time to read the following information carefully and feel free to ask if you would like more information or if there is anything that you do not understand. Please also feel free to discuss this with your friends, relatives and your GP. You do not have to accept this invitation and should only agree to take part if you want to.

What is the purpose of this study?

We are interested in factors associated with emotional distress in people living with chronic fatigue symptoms (PWCFS). These symptoms are experienced by people with diagnoses including Chronic Fatigue Syndrome (CFS), Myalgic Encephalomyelitis (ME), and Chronic fatigue and immune dysfunction syndrome (CFIDS).

Why is this research needed?

Emotional distress can be a common experience for people living with chronic fatigue symptoms. However, little is known about the factors associated with emotional distress. This means it is difficult to develop therapeutic interventions for emotional distress which may be experienced by people living with chronic fatigue symptoms.

Why have I been asked to take part?

The invitation to take part in the study does not mean that we think you have problems with emotional distress. We are inviting people to participate regardless of how they presently feel

The study aims to include at least 118 people between the ages of 18 and 75, who have received a clinical diagnosis of either Chronic Fatigue Syndrome (CFS), Myalgic Encephalomyelitis (ME) or Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS).

Do I have to take part?

No. It is up to you whether you agree to take part. If you do decide to take part, you will be asked to sign a consent form.

What will happen if I agree to take part?

You will be asked to complete a survey which will take around 20-30 minutes. You will be asked to complete this within two hours and can take breaks during if you need to do so. The online version of the survey has an option to save and continue.

You will be asked a series of questions about you (e.g. age/gender) and your symptoms (e.g. fatigue, low mood, worry. You will not be asked to identify yourself as an individual.

How will my data be used?

The University of Liverpool is the sponsor for this study based in the United Kingdom. The University will be using information from you in order to undertake this study. The University is responsible for looking after your information and using it properly. Under UK data protection legislation, the University acts as the Data Controller for personal data collected as part of the University's research. The Principal Investigator acts as the Data Processor for this study, and any queries relating to the handling of your personal data can be sent to peter.fisher@liverpool.ac.uk

The University processes personal data as part of its research and teaching activities in accordance with the lawful basis of ‘public task’, and in accordance with the University’s purpose of “advancing education, learning and research for the public benefit.”

Further information on how your data will be used can be found in the table below:

How will my data be collected?	Data will be collected through either an online or paper survey.
How will my data be stored?	Data from the online surveys will be stored on the Qualtrics server for a maximum of one week, before being transferred to a database on the University of Liverpool Secure Server. Data from paper surveys will be entered onto the same database on at least a monthly basis. Following this, they will be destroyed immediately. Paper surveys submitted to NHS clinics will be held securely until they are collected by the researcher.
How long will my data be stored for?	Data collected in this study may be held for up to 10 years.

What measures are in place to protect the security and confidentiality of my data?	Qualtrics stores data on a secure European Union server (which is a legal requirement for data collected from EU citizens).The only people who will have access to the data is the Researcher and the Primary Investigator. The University of Liverpool has a specific contract with Qualtrics. For the duration of the study, a database storing survey data and email addresses for the prize draw will be kept securely a University of Liverpool server. Email addresses will be used solely for the purposes of the prize draw or feedback on the outcome of the research if requested. Email addresses will be separated from survey data and stored on a password protected computer system, accessible to the Researchers only. They will be destroyed when they are no longer needed.
Will my data be anonymised?	Your data will be anonymous at the point of collection. Email addresses will not be linked to the data you submit when entered into the database. You will not be identifiable as an individual when we gather, analyse the data or write reports about the study.

How will my data be used?	Once the study is complete, we will analyse the results and publish it in academic journals. We will not identify you in any way when the results are published. Should you so wish, we will send you a short report of the findings of the study.
Who will have access to my data?	Information will not be revealed to anyone outside of the research team.
Will my data be archived for use in other research projects in the future?	No
How will my data be destroyed?	Data from paper surveys will be shredded immediately following entry to the secure database. The database will be deleted no later than ten years after completion of the study.

Expenses and / or payments

There are no payments for taking part. However, to thank participants for taking part we are offering the chance to enter a prize draw for one of ten £15 retail vouchers. Winners will be selected from random via computer software. Details will be given to those who have completed the surveys.

Are there any risks in taking part?

There are no known risks of taking part and the survey consists of surveys completed by lots of people living with chronic fatigue symptoms. However, some of the questions ask about negative emotions and symptoms which can be upsetting. You are under no obligation to complete the survey and can stop at any time.

If you become fatigued whist completing the survey over 20-30 minutes, there is an option to save your responses and continue when you are rested.

If completing the survey raises any concerns, there are several options to obtain further advice outlined below:

1) You could talk to your GP to discuss your concerns.
2) There several websites and organizations which provide information and advice about Chronic Fatigue Syndrome (CFS) / Myalgic Encephalomyelitis (ME). These include:

- Action for ME (https://www.actionforme.org.uk)
  Telephone: **0117 927 9551**

- The ME Association www.meassociation.org.uk
  Telephone: **0344 576 5326**

3) The NHS website https://www.nhs.uk/conditions/chronic-fatigue-syndrome-cfs/treatment/ also offers advice.

4) If completing the survey causes any discomfort, you can contact the Principal investigator Dr Peter Fisher, Senior Lecturer in Clinical Psychology:
Email: peter.fisher@liverpool.ac.uk
Telephone: 0151 794 4160

What are the possible benefits of taking part?

There are no immediate personal benefits. However, the data obtained from the survey may help to improve psychological treatments for PWCFS experiencing emotional distress.

What will happen to the results of the study?

The data obtained from the survey will be analysed and may be published in an academic journal. The results will also be written up as part of a thesis being conducted by a Clinical Psychology student. The write up of the study will not contain any information which could identify you.

What will happen if I want to stop taking part?

You can stop completing the survey at any point and choose not to submit it. If you do decide to submit the survey, your rights to access, change or move your information are limited. This is because we need to manage your information in specific ways in order for the research to be reliable and accurate. To safeguard your rights, we will use the minimum personally-identifiable information possible. Your data will be anonymous at the point of collection. It will therefore not be possible to identify your data in order to withdraw it from the study. Please therefore think carefully whether you wish to take part, before completing the survey.

You can find out more about how we use your information by contacting the Principle Investigator, Dr.Peter Fisher,
Email: peter.fisher@liverpool.ac.uk Telephone: 0151 794 4160

What if I am unhappy or if there is a problem?

If you are unhappy, or if there is a problem, please contact the Principle Investigator, Dr .Peter Fisher: email; peter.fisher@liverpool.ac.uk or telephone: 0151 794 4160 and we will try to help. If you remain unhappy or have a complaint which you feel you cannot come to us with then you should contact the Research Ethics and Integrity Office at ethics@liv.ac.uk. When contacting the Research Ethics and Integrity Office, please provide details of the name or description of the study (so that it can be identified), the researcher(s) involved, and the details of the complaint you wish to make.

The University strives to maintain the highest standards of rigour in the processing of your data. However, if you have any concerns about the way in which the University processes your personal data, it is important that you are aware of your right to lodge a complaint with the Information Commissioner's Office by calling 0303 123 1113

What if I want to ask questions not included in this information?

To raise any further questions, please feel free to contact the study Principal Investigator: Dr Peter Fisher on (0151-794-4160) / Peter.Fisher@liverpool.ac.uk or the Student Researcher Amelia Wright: amelia.wright@liverpool.ac.uk

Address: University of Liverpool, Whelan Building, Brownlow Hill,
Liverpool, L69 3GB.

Appendix K: Participant Consent Form

Participant consent form
Version 4. 24/1/19

UNIVERSITY OF LIVERPOOL

Participant Consent Form

Title of the research project: Emotional Distress and Chronic Fatigue Symptoms

In order to proceed with the study please read the following statements:

Please check / initial box:

1. I confirm that I have read and have understood the information sheet dated 12/07/2019 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and should I not wish to answer any particular question or questions, I am free to decline. ☐
3. I understand that the information I give will be anonymous at the point of collection. This means it will not be possible to identify my completed questionnaires. Because of this, I understand it is not possible to withdraw my results once I have submitted my anonymous information. ☐
4. I understand that should I choose to give my email address for either entry to the prize draw or feedback on the research, this will be separated from my survey responses and stored securely. ☐
5. I understand that should I chose to give my email address, this will be deleted within one month of either a) the prize draw or b) receiving feedback on the research (whichever comes first). ☐
6. I agree for the data I provide to be archived securely at the University of Liverpool's secure computer system. I understand that other authorised researchers will have access to this data. ☐
7. I agree to take part in the above study. ☐

Researcher(s): Amelia Wright, Dr.Peter Fisher, Dr.Gemma Cherry & Dr.Nita Baker

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IRAS project number: 253333

Emotional Distress and Chronic Fatigue Symptoms

Thank you for agreeing to complete this survey which will take around 20-30 minutes in total. You may take breaks if you need to. However, we ask that you complete the questions within a two-hour time period.

Demographics

Please tick appropriate answers:

Diagnosis and Symptoms

I confirm that I have received a clinical diagnosis of Myalgic Encephalomyelitis (ME)/ Chronic Fatigue Syndrome (CFS) by a qualified medical professional (e.g. GP, ME/CFS Specialist in an NHS CFS Clinic).

☐ Yes

I have been experiencing chronic fatigue symptoms for approximately…….years.

Gender:

☐ Female
☐ Male

Age: ……years

Other illnesses:

I have a clinical diagnosis of Depression

☐ Yes
☐ No

I have a clinical diagnosis of Fibromyalgia

☐ Yes
☐ No

I have a clinical diagnosis of Chronic Pain Syndrome

☐ Yes
☐ No

I have a clinical diagnosis of Irritable Bowel Syndrome.

☐ Yes
☐ No

The Research

How did you hear about this research?

☐ Through my CFS / ME Clinic
☐ Through a CFS / ME support group / online support group
☐ Other

Appendix M: Hospital Anxiety and Depression Scale

Please read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week.
Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick only one box in each section

I feel tense or 'wound up':
- Most of the time .....
- A lot of the time .....
- Time to time, Occasionally .....
- Not at all .....

I still enjoy the things I used to enjoy:
- Definitely as much .....
- Not quite so much .....
- Only a little .....
- Hardly at all .....

I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly .....
- Yes, but not too badly .....
- A little, but it doesn't worry me .....
- Not at all .....

I can laugh and see the funny side of things:
- As much as I always could .....
- Not quite so much now .....
- Definitely not so much now .....
- Not at all .....

Worrying thoughts go through my mind:
- A great deal of the time .....
- A lot of the time .....
- From time to time but not too often .
- Only occasionally .....

I feel cheerful:
- Not at all .....
- Not often .....
- Sometimes .....
- Most of the time .....

I can sit at ease and feel relaxed:
- Definitely .....
- Usually .....
- Not often .....
- Not at all .....

I feel as if I am slowed down:
- Nearly all the time .....
- Very often .....
- Sometimes .....
- Not at all .....

I get a sort of frightened feeling like 'butterflies' in the stomach:
- Not at all .....
- Occasionally .....
- Quite often .....
- Very often .....

I have lost interest in my appearance:
- Definitely .....
- I don't take so much care as I should
- I may not take quite as much care ..
- I take just as much care as ever .....

I feel restless as if I have to be on the move:
- Very much indeed .....
- Quite a lot ... .
- Not very much .....
- Not at all .....

I look forward with enjoyment to things:
- As much as ever I did .....
- Rather less than I used to .....
- Definitely less than I used to .....
- Hardly at all .....

I get sudden feelings of panic:
- Very often indeed .....
- Quite often ... .
- Not very often .....
- Not at all .....

I can enjoy a good book or radio or TV programme:
- Often .....
- Sometimes .....
- Not often .....
- Very seldom .....

Appendix N: Scoring for Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

GL assessment

Name: _____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

A	D			A	D
		I feel tense or 'wound up'	**I feel as if I am slowed down**		
3		Most of the time	Nearly all the time		3
2		A lot of the time	Very often		2
1		From time to time, occasionally	Sometimes		1
0		Not at all	Not at all		0
		I still enjoy the things I used to enjoy	**I get a sort of frightened feeling like 'butterflies' in the stomach**		
	0	Definitely as much	Not at all	0	
	1	Not quite so much	Occasionally	1	
	2	Only a little	Quite often	2	
	3	Hardly at all	Very often	3	
		I get a sort of frightened feeling as if something awful is about to happen	**I have lost interest in my appearance**		
3		Very definitely and quite badly	Definitely		3
2		Yes, but not too badly	I don't take as much care as I should		2
1		A little, but it doesn't worry me	I may not take quite as much care		1
0		Not at all	I take just as much care as ever		0
		I can laugh and see the funny side of things	**I feel restless as if I have to be on the move**		
	0	As much as I always could	Very much indeed	3	
	1	Not quite so much now	Quite a lot	2	
	2	Definitely not so much now	Not very much	1	
	3	Not at all	Not at all	0	
		Worrying thoughts go through my mind	**I look forward with enjoyment to things**		
3		A great deal of the time	As much as I ever did		0
2		A lot of the time	Rather less than I used to		1
1		Not too often	Definitely less than I used to		2
0		Very little	Hardly at all		3
		I feel cheerful	**I get sudden feelings of panic**		
	3	Never	Very often indeed	3	
	2	Not often	Quite often	2	
	1	Sometimes	Not very often	1	
	0	Most of the time	Not at all	0	
		I can sit at ease and feel relaxed	**I can enjoy a good book or radio or television programme**		
0		Definitely			
1		Usually	Often		0
2		Not often	Sometimes		1
3		Not at all	Not often		2
			Very seldom		3

Now check that you have answered all the questions

	A	D
TOTAL		

Appendix O: Chalder Fatigue Scale

We would like to know more about any problems you have had with feeling tired, weak or lacking in energy in the last month. Please answer ALL the questions by ticking the answer which applies to you most closely. If you have been feeling tired for a long while, then compare yourself to how you felt when you were last well. Please tick only one box per line.

	Less than usual	**No more than usual**	**More than usual**	**Much more than usual**
Do you have problems with tiredness?				
Do you need to rest more?				
Do you feel sleepy or drowsy?				
Do you have problems starting things?				
Do you lack energy?				
Do you have less strength in your muscles?				
Do you feel weak?				
Do you have difficulties concentrating?				
Do you make slips of the tongue when speaking?				
Do you find it more difficult to find the right word?				
	Better than usual	**No worse than usual**	**Worse than usual**	**Much worse than usual**
How is your memory?				

Cella, M. and T. Chalder (2010). "Measuring fatigue in clinical and community settings." J Psychosom Res 69(1): 17-22

Appendix P: The metacognitions Questionnaire-30 (MCQ-30)

Adrian Wells & Samantha Cartwright-Hatton

This questionnaire is concerned with beliefs people have about their thinking.
Listed below are a number of beliefs that people have expressed. Please read each item and say how much you generally agree with it by circling the appropriate number.
Please respond to all items, there are no right or wrong answers.

		Do not agree	Agree slightly	Agree moderately	Agree very much
1.	Worrying helps me to avoid problems in the future	1	2	3	4
2.	My worrying is dangerous for me	1	2	3	4
3.	I think a lot about my thoughts	1	2	3	4
4.	I could make myself sick with worrying	1	2	3	4
5.	I am aware of the way my mind works when I am thinking through a problem	1	2	3	4
6.	If I did not control a worrying thought, and then it happened, it would be my fault	1	2	3	4
7.	I need to worry in order to remain organised	1	2	3	4
8.	I have little confidence in my memory for words and names	1	2	3	4
9.	My worrying thoughts persist, no matter how I try and stop them	1	2	3	4
10.	Worrying helps me to get things sorted out in my mind	1	2	3	4
11.	I cannot ignore my worrying thoughts	1	2	3	4
12.	I monitor my thoughts	1	2	3	4
13.	I should be in control of my thoughts all of the time	1	2	3	4

		Do not agree	Agree slightly	Agree moderately	Agree very much
14.	My memory can misled me at times	1	2	3	4
15.	My worrying could make me go mad	1	2	3	4
16.	I am constantly aware of my thinking	1	2	3	4
17.	I have a poor memory	1	2	3	4
18.	I pay close attention to the way my mind works	1	2	3	4
19.	Worrying helps me cope	1	2	3	4
20.	Not being able to control my thoughts is a sign of weakness	1	2	3	4
21.	When I start worrying, I cannot stop	1	2	3	4
22.	I will be punished for not controlling certain thoughts	1	2	3	4
23.	Worrying helps me to solve problems	1	2	3	4
24.	I have little confidence in my memory for places	1	2	3	4
25.	It is bad to think certain thoughts	1	2	3	4
26.	I do not trust my memory	1	2	3	4
27.	If I could not control my thoughts, I would not be able to function	1	2	3	4
28.	I need to worry, in order to work well	1	2	3	4
29.	I have little confidence in my memory for actions	1	2	3	4
30.	I constantly examine my thoughts	1	2	3	4

Please ensure that you have responded to all items – Thank You.

Appendix Q: The Cognitive-Attentional Syndrome 10 (CAS-10)

1. **How much time in the last week have you found yourself dwelling on or worrying about problems (e.g. health, family, finances)? (Circle a number below)**

0	10	20	30	40	50	60	70	80	90	100

None of the time — **Half of the time** — **All of the time**

2. **How much time in the last week have you found yourself analysing your feelings/symptoms or questioning why did this happen to me? (Circle a number below)**

0	10	20	30	40	50	60	70	80	90	100

None of the time — **Half of the time** — **All of the time**

3. **How much time in the last week have you been focusing attention on the things you find threatening (e.g. symptoms, thoughts, bodily checking)? (Circle a number below)**

0	10	20	30	40	50	60	70	80	90	100

None of the time — **Half of the time** — **All of the time**

4. **How much time in the last week have you avoided activity or certain situations? (Circle a number below)**

0	10	20	30	40	50	60	70	80	90	100

None of the time — **Half of the time** — **All of the time**

5. **How much time in the last week have you tried not to think certain thoughts? (Circle a number below)**

0	10	20	30	40	50	60	70	80	90	100

None of the time — **Half of the time** — **All of the time**

6. **How much time in the last week have you used alcohol to cope with thoughts/feelings? (Circle a number below)**

0	10	20	30	40	50	60	70	80	90	100

None of the time — **Half of the time** — **All of the time**

7. How much do you believe that worrying or dwelling on thoughts is uncontrollable? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100

Not at all — **Fifty percent certain** — **Completely certain this is true**

8. How much do you believe that worrying or dwelling on thoughts is harmful? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100

Not at all — **Fifty percent certain** — **Completely certain this is true**

9. How much do you believe that worrying is helpful? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100

Not at all — **Fifty percent certain** — **Completely certain this is true**

10. How much do you believe that anticipating problems will keep you safe? (Circle a number below)

0	10	20	30	40	50	60	70	80	90	100

Not at all — **Fifty percent certain** — **Completely certain this is true**

Appendix R: Participant debrief form

UNIVERSITY OF LIVERPOOL

DEBRIEF FORM

Title Study: Emotional Distress and Chronic Fatigue Symptoms

Thank you for completing the survey.

The aim of this study is to understand factors which may increase emotional distress experienced by people with Chronic Fatigue Symptoms (PWCFS). We are interested in whether thought *processes* (not *what* people think) may increase this emotional distress, regardless of the level of fatigue experienced.

We hope to be in a better position following this study to develop more effective therapeutic interventions for PWCFS who experience emotional distress.

If completing the survey raises any concerns, then there are several options to obtain further advice outlined below:

- You could talk to your GP to discuss your concerns.

- There several websites and organizations which provide information and advice about CFS / ME. These include:

Action for ME (https://www.actionforme.org.uk)

The ME Association www.meassociation.org.uk

In addition, please see the following NHS website for further information regarding treatment:
https://www.nhs.uk/conditions/chronic-fatigue-syndrome-cfs/treatment/

If completing the survey did lead to you feeling any discomfort, you can also contact the Principal investigator Dr Peter Fisher, Senior Lecturer in Clinical Psychology. Email: peter.fisher@liverpool.ac.uk
Telephone: 0151 794 4160

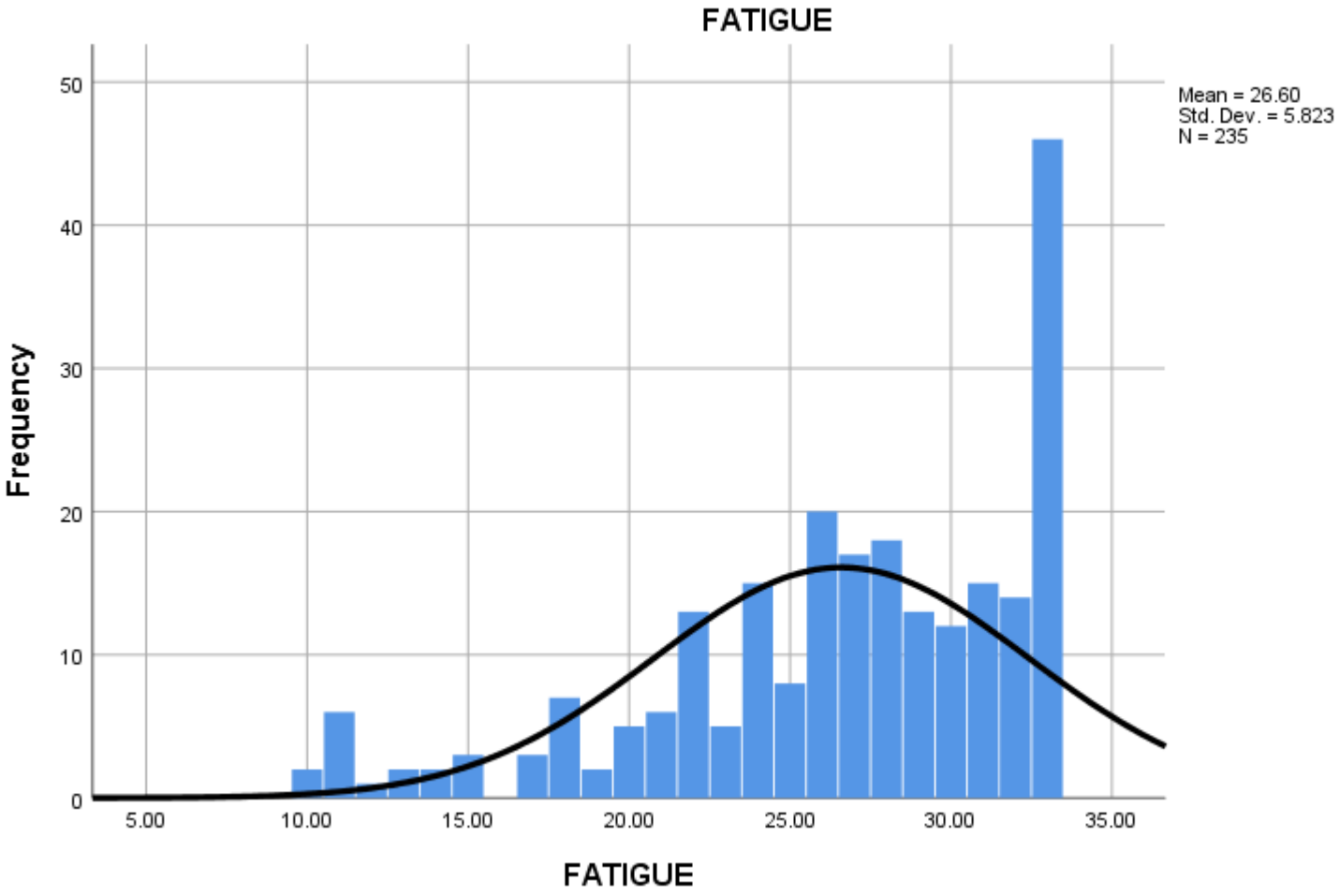
Feedback on the study and the overall results will be available from the Student Investigator, Amelia Wright upon request from October 2020. Please email: amelia.wright@liverpool.ac.uk

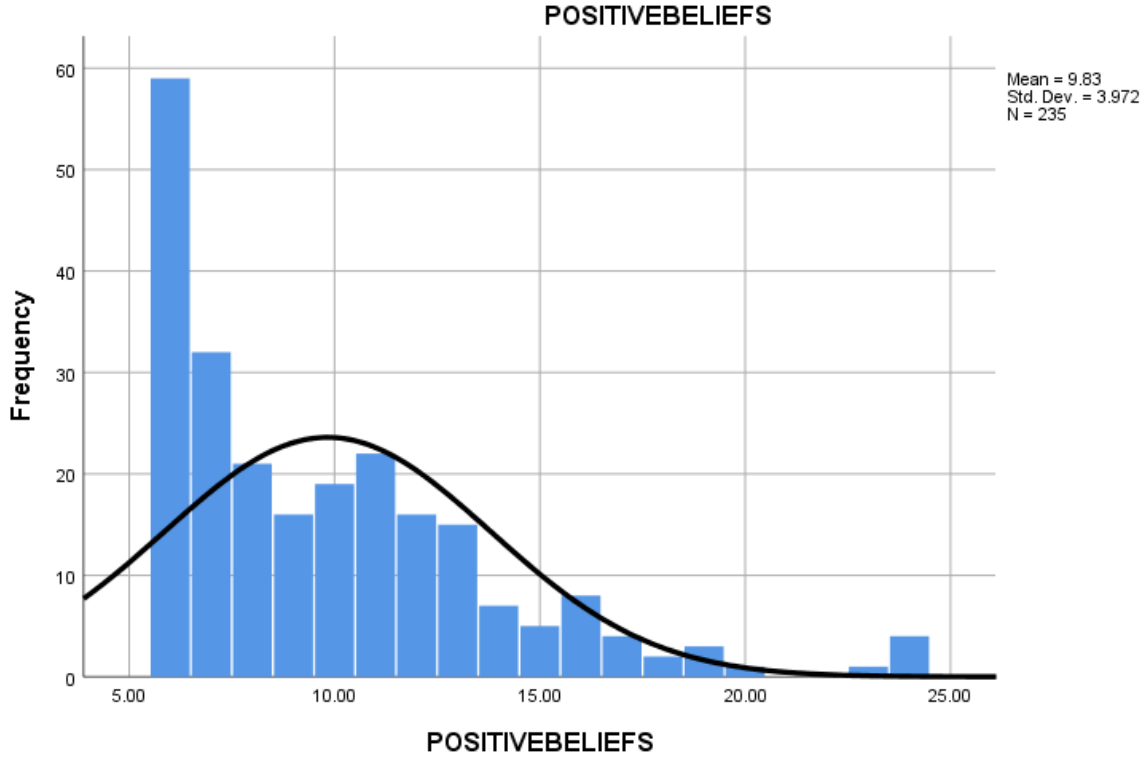
Appendix S: Distributions and Skewness and Kurtosis Statistics

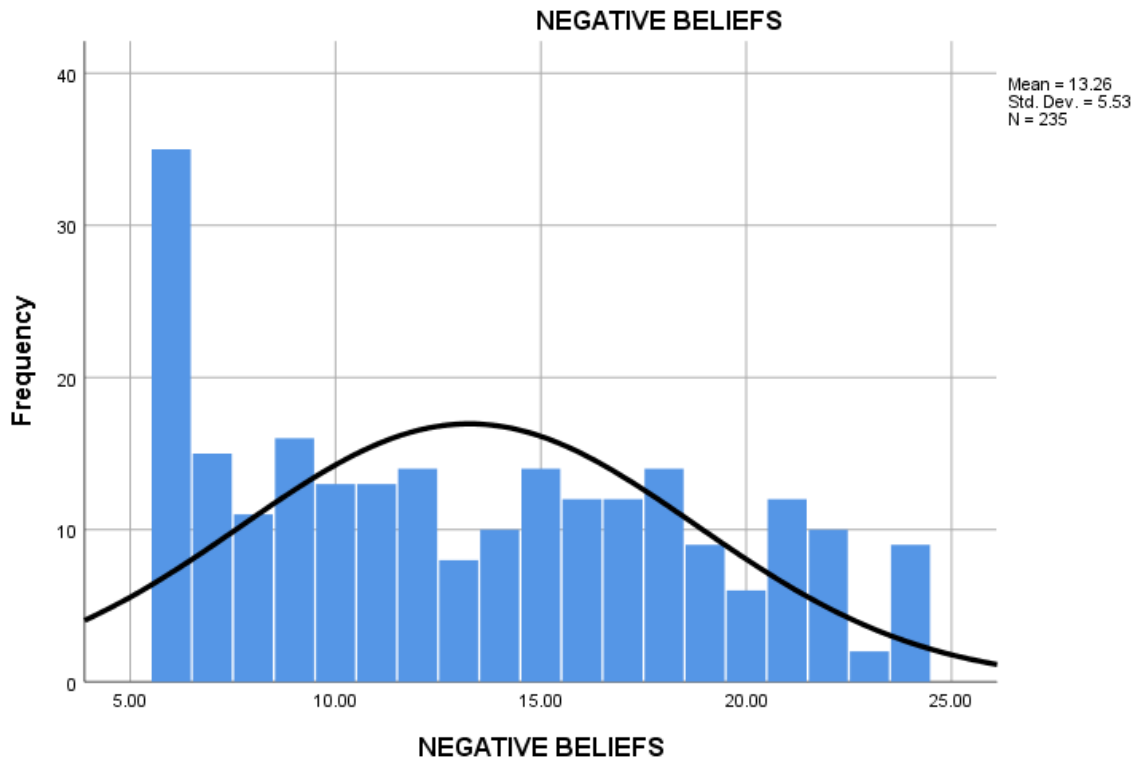
Statistics

		FATIGUE	DISTRESS	ANXIETY	DEPRESSION	CAS1TO6	POSITIVE BELIEFS	NEGATIVE BELIEFS	LACKOF COG CONF	COG SELF CONSC	NEED CONTOL THOUGHT	TIME SINCE ONSET	GENDER	AGE
N	Valid	235	235	235	235	235	235	235	235	235	235	235	235	235
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean		26.5957	19.9319	10.3106	9.6213	234.5106	9.8298	13.2553	15.4894	14.8468	10.6085	13.2234	1.92	43.3787
Median		28.0000	21.0000	11.0000	10.0000	250.0000	9.0000	13.0000	15.0000	15.0000	10.0000	10.0000	2.00	44.0000
Mode		33.00	23.00[a]	13.00	9.00	330.00	6.00	6.00	12.00[a]	12.00	6.00	5.00	2	47.00
Std. Deviation		5.82310	9.39106	5.58628	4.75974	140.75527	3.97169	5.52952	5.32480	4.32864	4.26774	9.55014	.273	12.71537
Skewness		-.975	-.183	-.182	.003	-.033	1.319	.275	.056	.275	1.046	1.074	-3.095	.048
Std. Error of Skewness		.159	.159	.159	.159	.159	.159	.159	.159	.159	.159	.159	.159	.159
Kurtosis		.451	-.769	-.981	-.631	-1.030	1.841	-1.127	-1.116	-.726	.601	.795	7.643	-.830
Std. Error of Kurtosis		.316	.316	.316	.316	.316	.316	.316	.316	.316	.316	.316	.316	.316

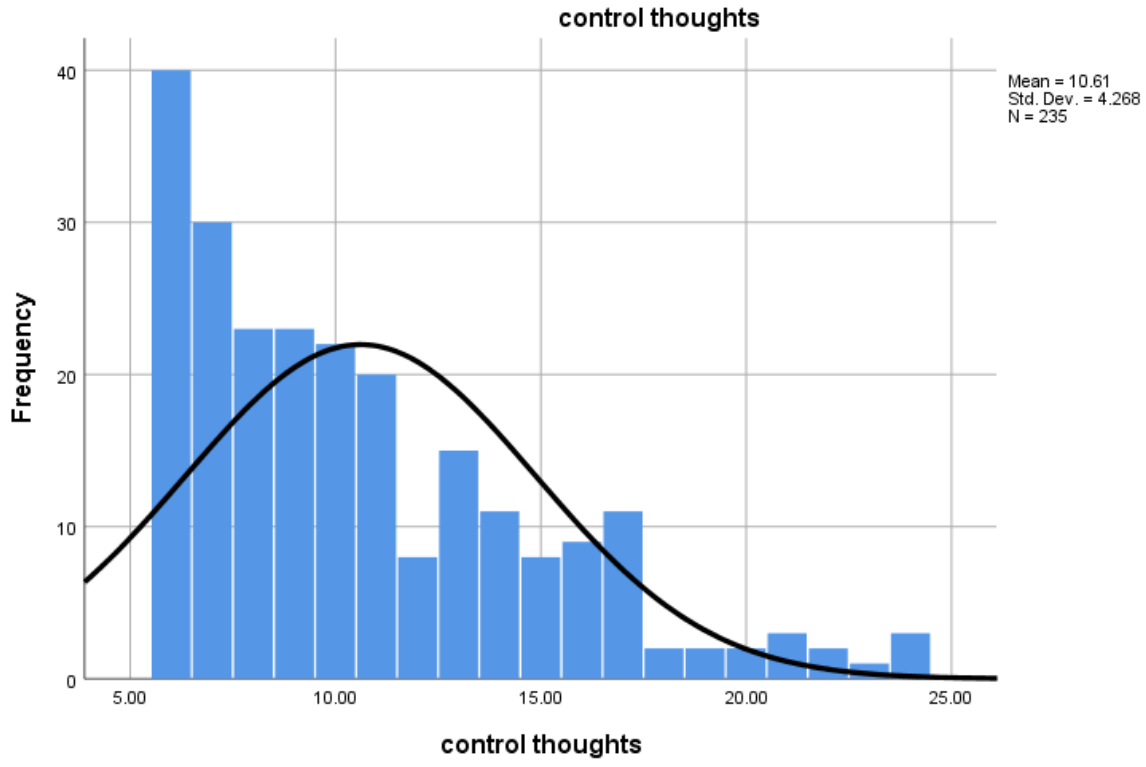
a. Multiple modes exist. The smallest value is shown

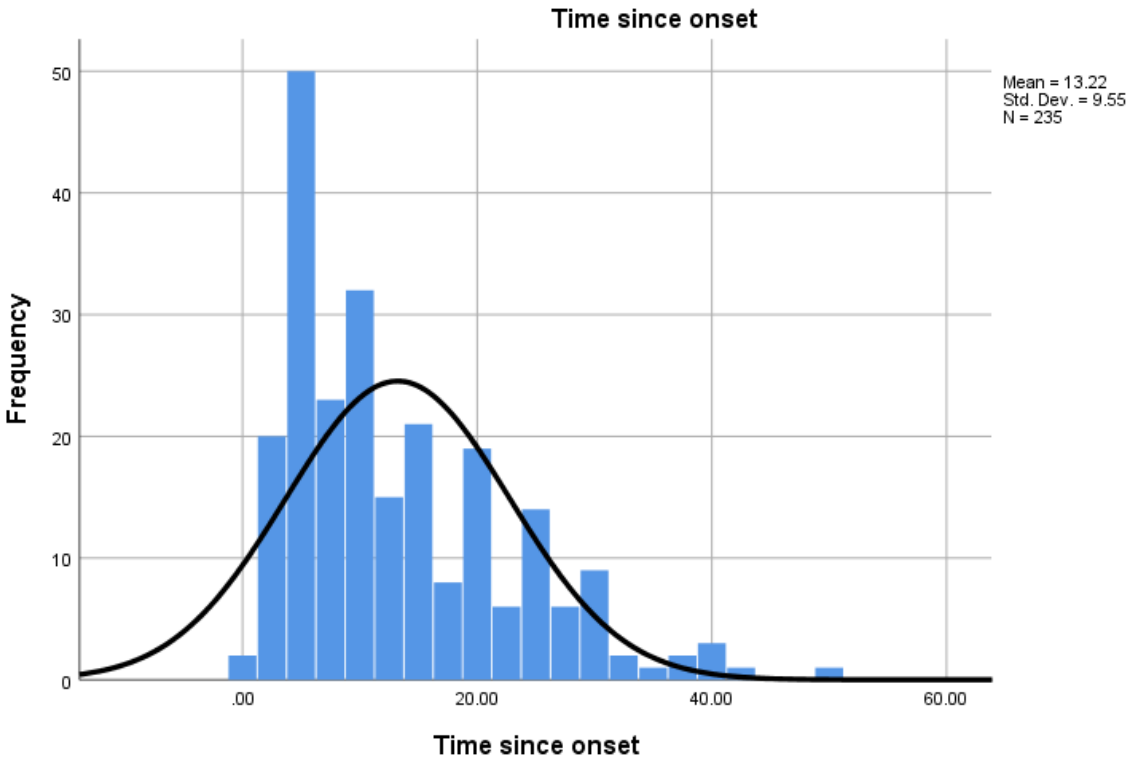

FATIGUE
Mean = 26.60
Std. Dev. = 5.823
N = 235
Frequency
50
40
30
20
10
0
5.00
10.00
15.00
20.00
25.00
30.00
35.00
FATIGUE


POSITIVEBELIEFS
Mean = 9.83
Std. Dev. = 3.972
N = 235
Frequency
60
50
40
30
20
10
0
5.00
10.00
15.00
20.00
25.00
POSITIVEBELIEFS

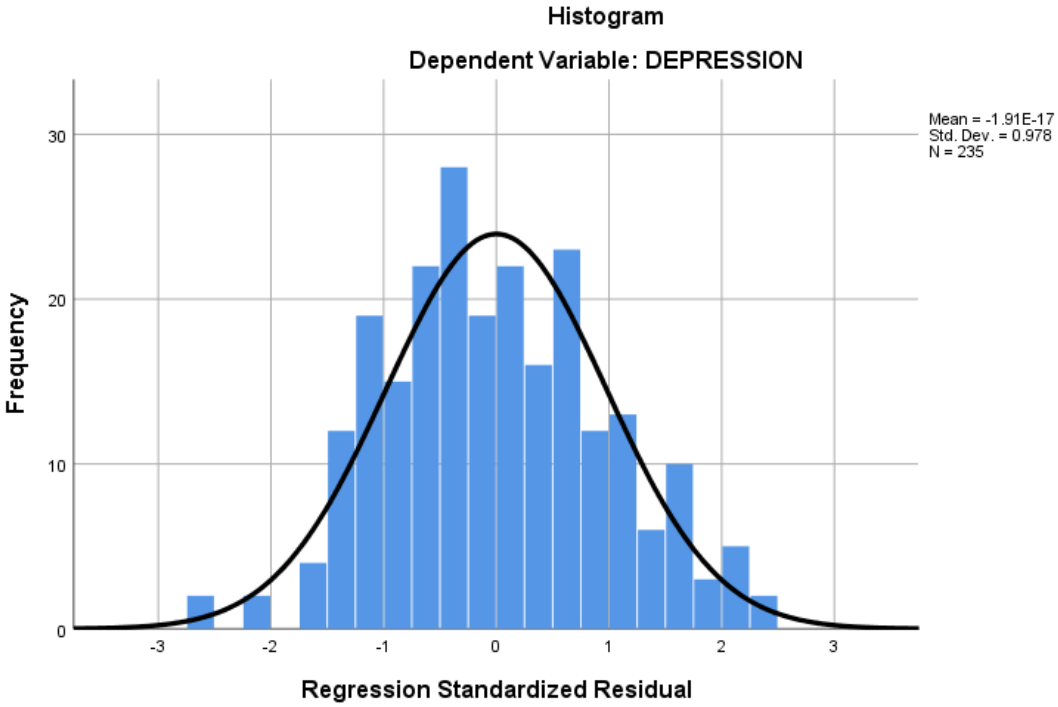


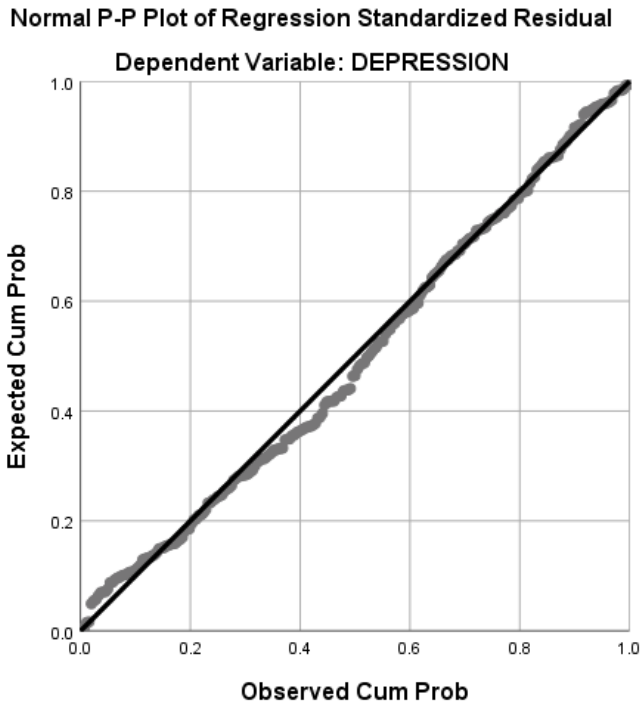
Note: Negative metacognitive beliefs -treated as sked due to shape of distribution curve.

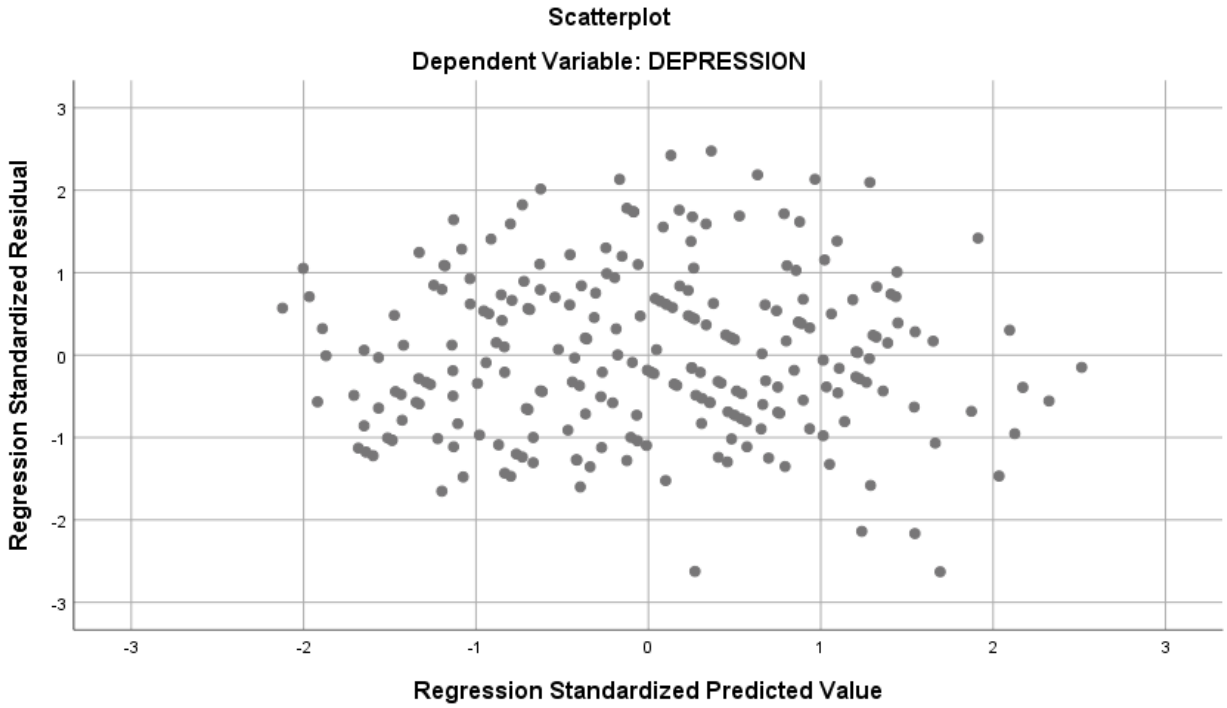



Time since onset
Mean = 13.22
Std. Dev. = 9.55
N = 235
Frequency
50
40
30
20
10
0
.00
20.00
40.00
60.00
Time since onset

Appendix T: Assessment of Regression Assumptions.



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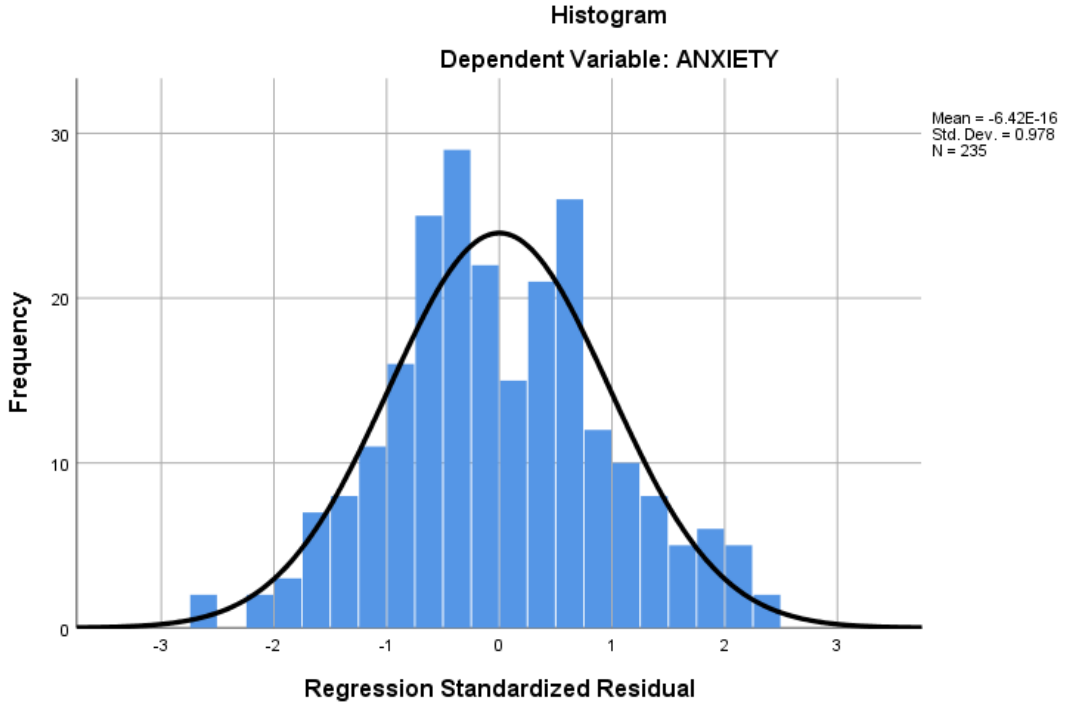
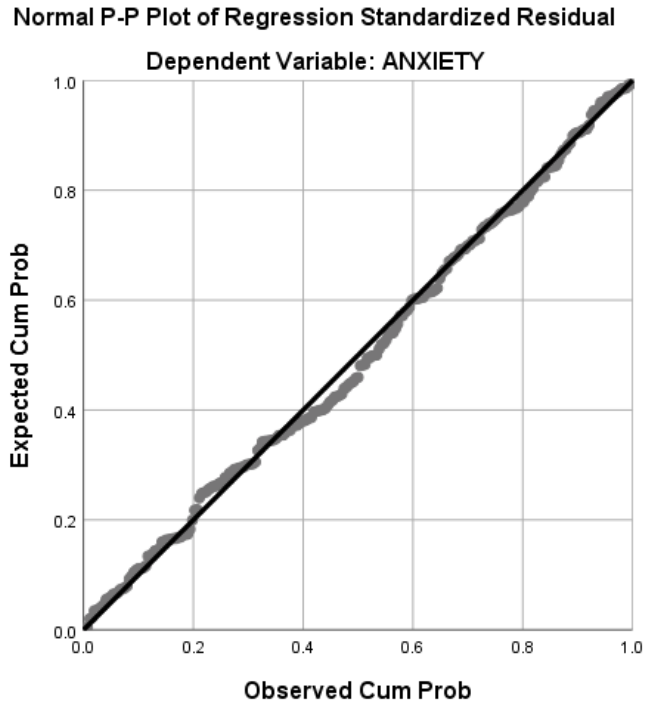
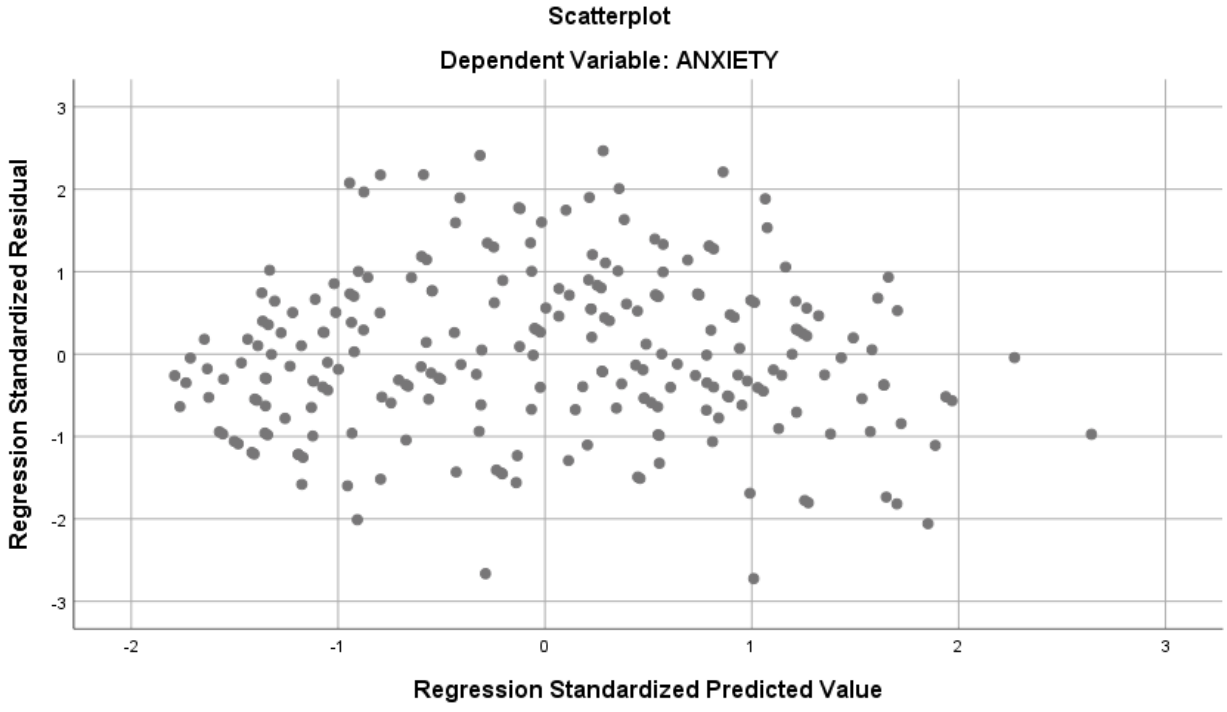
Regression Standardized Residual
Regression Standardized Predicted Value
3
2
1
0
-1
-2
-3


Histogram
Dependent Variable: ANXIETY
Mean = -6.42E-16
Std. Dev. = 0.978
N = 235
Frequency
Regression Standardized Residual
30
20
10
0
-3
-2
-1
0
1
2
3


Normal P-P Plot of Regression Standardized Residual
Dependent Variable: ANXIETY
Expected Cum Prob
Observed Cum Prob
0.0
0.2
0.4
0.6
0.8
1.0


Scatterplot
Dependent Variable: ANXIETY
Regression Standardized Residual
Regression Standardized Predicted Value
3
2
1
0
-1
-2
-3